



WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

PCT

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/11, 15/00, 15/63, C07H 21/02, 21/04	A1	(11) International Publication Number: WO 00/04140	(43) International Publication Date: 27 January 2000 (27.01.00)
---	----	---	--

(21) International Application Number: PCT/US99/15849

(22) International Filing Date: 14 July 1999 (14.07.99)

(30) Priority Data:
60/092,921 15 July 1998 (15.07.98)
60/092,922 15 July 1998 (15.07.98)
60/092,956 15 July 1998 (15.07.98)
US
US

(71) Applicant (for all designated States except US): HUMAN
GENOME SCIENCES, INC. [US/US]; 9410 Key West
Avenue, Rockville, MD 20850 (US).

(72) Inventors; and
(75) Inventors/Applicants (for US only): RUBEN, Steven, M.
[US/US]; 18528 Heritage Hills Drive, Olney, MD 20832
(US); KOMATSOU, George [US/US]; 9518 Garwood
Street, Silver Spring, MD 20901 (US); DUAN, Roxanne,
D. [US/US]; 5515 Northfield Road, Bethesda, MD 20817
(US); ROSEN, Craig, A. [US/US]; 22400 Rolling Hill Road,
Laytonsville, MD 20882 (US); MOORE, Paul, A. [US/US];
19005 Leatherbank Drive, Germantown, MD 20874 (US);
SHI, Yang-gu [CN/US]; Apartment 102, 437 West Side
Drive, Gaithersburg, MD 20878 (US); LAFLEUR, David,
W. [US/US]; 3142 Quesada Street, N.W., Washington, DC
20015 (US); EBNER, Reinhard [DE/US]; 9906 Shelburne

(74) Agents: BROOKES, A., Anders et al.; Human Genome
Sciences, Inc., 9410 Key West Avenue, Rockville, MD
20850 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR,
BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, FR, GB, GE,
GR, GM, GU, HK, HU, ID, IL, IN, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, LY, MD, MG, MK, MN,
MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
SL, SM, ST, SV, TH, TJ, TM, TR, TT, UA, UG, US, UZ, VA, VU, ZW,
ZM, ZY). Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI,
FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE,
SN, TD, TG).

Published
With international search report.

(54) Title: 71 HUMAN SECRETED PROTEINS

(57) Abstract

The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.

NTKB 1712
222
Fig 205
#315, 6
#315 ⇒ SEQ ID 118
#316 ⇒ SEQ ID 119
(#317) 177

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

FOR THE PURPOSES OF INFORMATION ONLY

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MR	Mauritania	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Cote d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China			PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

71 Human Secreted Proteins

Field of the Invention

This invention relates to newly identified polynucleotides and the

polypeptides encoded by these polynucleotides, uses of such polynucleotides and polypeptides, and their production.

Background of the Invention

Unlike bacterium, which exist as a single compartment surrounded by a

membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or

organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to

target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a

leader sequence, directs a class of proteins to an organelle called the endoplasmic

reticulum (ER). The ER separates the membrane-bounded proteins from all other

types of proteins. Once localized to the ER, both groups of proteins can be further

directed to another organelle called the Golgi apparatus. Here, the Golgi distributes

the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes,

and the other organelles.

Proteins targeted to the ER by a signal sequence can be released into the

extracellular space as a secreted protein. For example, vesicles-containing secreted

proteins can fuse with the cell membrane and release their contents into the

extracellular space - a process called exocytosis. Exocytosis can occur constitutively

or after receipt of a triggering signal. In the latter case, the proteins are stored in

secretory vesicles (or secretory granules) until exocytosis is triggered. Similarly,

proteins residing on the cell membrane can also be secreted into the extracellular

space-by-proteolytic cleavage of a "linker" holding the protein to the membrane.

Despite the great progress made in recent years, only a small number of genes

encoding human secreted proteins have been identified. These secreted proteins

include the commercially valuable human insulin, interferon, Factor VIII, human

5 growth hormone, tissue plasminogen activator, and erythropoietin. Thus, in light of the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical disorders by using secreted proteins or the genes that encode them.

Summary of the Invention

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, and recombinant methods for producing the polypeptides and

10 polynucleotides. Also provided are diagnostic methods for detecting disorders related to the polypeptides, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying binding partners of the polypeptides.

15

Detailed Description

Definitions

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

20

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated

polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide.

25

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins-released into the extracellular space

30 without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing

to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

In specific embodiments, the polynucleotides of the invention are less than 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, or 7.5 kb in length. In a further embodiment, polynucleotides of the invention comprise at least 15 contiguous nucleotides of the coding sequence, but do not comprise all or a portion of any intron. In another embodiment, the nucleic acid comprising the coding sequence does not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene in the genome).

10 As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As

25 shown in Table I, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an

overnight incubation at 42° C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH₂PO₄; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above,

due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA-clone).

The polynucleotide of the present invention can be composed of any

polynucleotide or polydeoxynucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of

- single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.
- The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation,

gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seftier et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992). "SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)

Polynucleotides and Polypeptides of the Invention

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 1

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the

following amino acid sequence:

30 PFCSGFFPSLWYILPFIENVSDLWMSGSLSGCALPFCLXVFFLTVSPSAVGLLXF
AGGPLQTLFAWVSPVEAAEQQRLLPVLSSGSFVSEGTCCMPARALLYEVVG

PYWEIPPSQDTRRSCTYLRQSDP (SEQ ID NO: 195). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in pancreas islet cell tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as

5 reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the pancreas, including cancer and diabetes. Similarly,

polypeptides and antibodies directed to these polypeptides are useful in providing

10 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the pancreas,

expression of this gene at significantly higher or lower levels is routinely detected in

certain tissues or cell types (e.g., endocrine, cancerous, or wounded tissues) or bodily

fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another

tissue or cell sample taken from an individual having such a disorder, relative to the

15 standard gene expression level, i.e., the expression level in healthy tissue or bodily

fluid from an individual not having the disorder.

The tissue distribution in tumors of pancreatic islet cells indicates that

polynucleotides and polypeptides corresponding to this gene are useful for diagnosis,

treatment and intervention of such tumors, in addition to other endocrine or

20 gastrointestinal tumors where expression has been indicated. Furthermore, the protein

may also be used to determine biological activity, to raise antibodies, as tissue

markers, to isolate cognate ligands or receptors, to identify agents that modulate their

interactions, in addition to its use as a nutritional supplement. Protein, as well as,

antibodies directed against the protein may show utility as a tumor marker and/or

25 immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly

available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:11 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically

30 excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1099 of SEQ ID NO:11, b is an integer of 15 to 1113, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.

5

FEATURES OF PROTEIN ENCODED BY GENE NO: 2

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

HEGSCRAPGFSAHKGRGCPSPRMTLPSRALASLGVGWGMLRLNQVTVSCG
GSRWSSRVATLGAFSWVGVALVLQPSGGGLTSPSEGCWEGELALAVLRA
PGGSPS (SEQ ID NO: 196). Polynucleotides encoding these polypeptides are also provided.

15

This gene is expressed equally in in .

Therefore, polynucleotides and polypeptides of the invention are useful as

reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic disorders, particularly leukemia. Similarly,

20

polypeptides and antibodies directed to these polypeptides are useful in providing

immunological probes for differential identification of the tissue(s) or cell type(s). For

a number of disorders of the above tissues or cells, particularly of the vascular and

immune systems, expression of this gene at significantly higher or lower levels is

routinely detected in certain tissues or cell types (e.g., immune, hemolymphoid,

25 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,

synovial fluid and spinal fluid) or another tissue or cell sample taken from an

individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the

disorder.

Preferred polypeptides of the present invention comprise immunogenic

epitopes shown in SEQ ID NO: 104 as residues: Gly-29 to Ser-35, Ser-63 to Cys-68.

Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in hemangioendothelioma, breast lymph node, and bone

marrow indicates that polynucleotides and polypeptides corresponding to this gene

are useful for the treatment and diagnosis of hematopoietic related disorders such as

anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells

are important in the production of cells of hematopoietic lineages. Representative uses

are described in the "Immune Activity" and "infectious disease" sections below, in

Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. The uses include

bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow

reconstitution, radiotherapy or chemotherapy of neoplasia.

The gene product may also be involved in lymphopoiesis, therefore, it can be

used in immune disorders such as infection, inflammation, allergy, immunodeficiency

etc. In addition, this gene product may have commercial utility in the expansion of

stem cells and committed progenitors of various blood lineages, and in the

differentiation and/or proliferation of various cell types. Furthermore, the protein may

also be used to determine biological activity, to raise antibodies, as tissue markers, to

isolate cognate ligands or receptors, to identify agents that modulate their interactions,

in addition to its use as a nutritional supplement. Protein, as well as, antibodies

directed against the protein may show utility as a tumor marker and/or

immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly

available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO: 12 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 969 of SEQ ID NO: 12, b is an

integer of 15 to 983, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 3

5 The translation product of this gene shares sequence homology with the Drosophila melanogaster slit protein, a secreted protein that contains both an EGF domain and Leucine Rich Repeat domains. It is thought to be important in the development of midline glia and commissural axon pathways (See e.g., Rothberg et al. Genes Dev. 4:2169-87 (1990); which is hereby incorporated by reference herein).

10 This gene is expressed primarily in human hippocampus.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, and developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurological system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neurological, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or

bodily fluid from an individual not having the disorder.

25 The tissue distribution within human hippocampus combined with the homology to the Drosophila slit protein, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and

"Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease,

Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating

diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal

cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia,

mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning

5 disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in

feeding, sleep patterns, balance, and preception. In addition, the gene or gene product

may also play a role in the treatment and/or detection of developmental disorders

associated with the developing embryo, sexually-linked disorders, or disorders of the

cardiovascular system. In addition, elevated expression of this gene product in regions

10 of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation,

neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or

survival. Furthermore, the protein may also be used to determine biological activity,

to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to

15 identify agents that modulate their interactions, in addition to its use as a nutritional

supplement. Protein, as well as, antibodies directed against the protein may show

utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly

available and accessible through sequence databases. Some of these sequences are

20 related to SEQ ID NO:13 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general

25 formula of a-b, where a is any integer between 1 to 959 of SEQ ID NO:13, b is an

integer of 15 to 973, where both a and b correspond to the positions of nucleotide

residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 4

30 In another embodiment, polypeptides comprising the amino acid sequence of
the open reading frame upstream of the predicted signal peptide are contemplated by

the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

IPLTLPGIFLLIRLFWRLGQSGPGKLVLPQFCCGCAVISGHCVPFRGMPSW
LPGCFVLLCLVAVGCGQLREWGVGVSAGLLALPHLQLVLMRGRLISGC

5 (SEQ ID NO: 197). Polynucleotides encoding these polypeptides are also provided. The gene encoding the disclosed cDNA is believed to reside on chromosome

16. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 16.

10 This gene is expressed in KMH2 cells, osteoblasts, fetal spleen, Jurkat membrane bound polysomes, breast, and cerebellum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer, immune, and skeletal disorders. Similarly, polypeptides and

15 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of

disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain

20 tissues or cell types (e.g., immune, skeletal, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another

tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy-tissue-or-bodily

fluid from an individual not having the disorder. The tissue distribution in KMH2 cells, osteoblasts, and fetal spleen indicates

25 that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in

Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Expression of this gene product in fetal spleen and T-cells indicates a role in the regulation of the

30 proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved

in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses).

5 Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory

bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and

10 tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, scleroderma and tissues. Moreover, the protein may represent a secreted

factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have

commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell

types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify

20 agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly

available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:14 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

30 formula of a-b, where a is any integer between 1 to 1444 of SEQ ID NO:14, b is an

integer of 15 to 1458, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 5

5 The translation product of this gene shares sequence homology with

phospholipase A2 which cleaves fatty acids from carbon 2 of glycerol (ref. Prosite pattern documentation for PS2_HIS). Many snake venoms contain phospholipase A2, which prevents transmission of nerve impulses to muscles by blocking the release of acetylcholine from the neuron. Therefore, included in this invention as preferred domains are Phospholipase A2 histidine active site domains, which were identified

10 using the Prosite analysis tool (Swiss Institute of Bioinformatics). Phospholipase A2 is an enzyme which releases fatty acids from the second carbon group of glycerol. Structurally, PA2's are small and rigid proteins of 120 amino-acid residues that have

15 four to seven disulfide bonds. PA2 binds a calcium ion which is required for activity. The side chains of two conserved residues, a histidine and an aspartic acid, participate in a catalytic network. Two different signature patterns for PA2's were developed.

The first is centered on the active site histidine and contains three cysteines involved in disulfide bonds. The consensus pattern is as follows: C-C-x(2)-H-x(2)-C [H is the

active site residue].

20 Preferred polypeptides of the invention comprise a Phospholipase A2 histidine

active site domain selected from the following amino acid sequences: CCNQHDFRC

(SEQ ID NO: 199), SLTKCCNQHDFRCYET (SEQ ID NO: 200), and/or

LTKCCNQHDFRCYETCG (SEQ ID NO: 201). Polynucleotides encoding these

25 polypeptides are also provided. Further preferred are polypeptides comprising the

Phospholipase A2 histidine active site domain of the sequence listed in Table 1 for

this gene, and at least 5, 10, 15, 20, 25, 30, 50, or 75 additional contiguous amino acid residues of this referenced sequence. The additional contiguous amino acid residues is

N-terminal or C-terminal to the Phospholipase A2 histidine active site domain.

Alternatively, the additional contiguous amino acid residues is both N-terminal and

30 C-terminal to the Phospholipase A2 histidine active site domain, wherein the total N- and C-terminal contiguous amino acid residues equal the specified number. The

above preferred polypeptide domain is characteristic of a signature specific to Phospholipase A2 proteins. Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with Phospholipase A2 proteins. Such activities are known in the art, some of which are described elsewhere herein, or see, for example, McIntosh, et al. J. Biol. Chem. 270 (8), 3518-3526 (1995), incorporated herein by reference.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

GPAGKEAWIWSWLLPSPGAPAPLPASWSWGLCGDAPR
 AARGPVEFGAARMALLSRPALTLLLLMAAVVRQCQEQAQTDDWRATLKTI
 RNGVHKIDITYNAALDLLGGBDGLCQYKCSDSGSKPFRYGYKPSPPNGCGSP
 LFGXHLNIGIPSLTRCCNQHDRRCYETCGGSKSKNDCEEFQYCLSKICRDVQKTL
 15 GLTQHVQACEFTVELLFDVSVIHLGCKPYLDQSRAACRCHYEKKTDL (SEQ ID
 NO: 198). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4.

20 This gene is expressed in a variety of cell types with no single type

predominating.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders, or metabolism disorders, specifically phospholipase A2 deficiencies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above

tissues or cells, particularly of the neuromuscular system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., pancreas, cancerous and wounded tissues) or bodily fluids (e.g., bile, lymph,

serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 107 as residues: Gln-23 to Asp-30, Lys-66 to Cys-87.

Polynucleotides encoding said polypeptides are also provided.

The ubiquitous tissue distribution and homology to phospholipase A2 indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis
10 and treatment of neuromuscular disorders. Alternatively, considering the activity of phospholipase A2 as a block for neuro- transmission may suggest that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette
15 Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked
20 disorders, or disorders of the cardiovascular system. Alternatively, the homology to Phospholipase A2 proteins may indicate a potential use for the protein product of this gene in diagnosis, treatment and/or prevention of metabolism disorders, specifically deficiencies in Phospholipase A2. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate
25 ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
30 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:15 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
 5 formula of a-b, where a is any integer between 1 to 1991 of SEQ ID NO:15, b is an integer of 15 to 2005, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 6

10 In a specific embodiment polypeptides of the invention comprise the following amino acid sequence:

GTSSARPRGALPGGSAPSAPHGQLPGRAQPAPVSGPPPTSGLCHFDPAAPWPL
 WPGPWQLPPHPQDWPAHPDIPQDWVSFLRSFGQLTLCPRNGTVTGKWRGSH
 VVGLLTTLNFGDGPDRNKTRTFQATVLGSQMGLKGSSAGQLVLITARVTTER
 15 TAGTCLYFSAVPGILPSSQPPISCSEEGAGNATLSPRMGEECVSVWSHEGLVLT
 KLLTSEELALCGSRLLVLGSFLLFCGLLCCVTAMCFHPRRESHWSRTRL
 (SEQ ID NO: 202). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by
 20 the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

ARAPPGPEGLSPEAQPLLPMGNCQAGHNLHLCLAHHPPLVCATLILLGLS
 GLGLGSFLLTHRTGLRT LTSPRTGSLF (SEQ ID NO: 203). Polynucleotides
 encoding these polypeptides are also provided.

25 This gene is expressed in a wide variety of tissue types including testes, cerebellum, dendritic cells, breast cancer, umbilical vein endothelial cells, epididymus, corpus colosum, chronic synovitis, liver hepatome, normal breast, osteoblasts, melanocytes, B cell lymphomas, and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as
 30 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, cancer, particularly of endothelial tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system,

5 expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., endothelial, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in

10 healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 108 as residues: Thr-52 to Gly-57. Polynucleotides encoding said polypeptides are also provided.

Expression within embryonic tissue and other cellular sources marked by

15 proliferating cells indicates that the protein product of this gene may play a role in the regulation of cellular division and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Additionally, the expression

20 in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic

25 development also relies on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain

30 neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have

applications in the adult for tissue-regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:16 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 929 of SEQ ID NO:16, b is an integer of 15 to 943, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 7

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

RFLSVXPQXEVFLLHPCVCFXGGHPSLLPDCRAVGGGWEAPRCCLHEALC
 QSLGCKAEEIVSVSESSAQRCWYLLRGRKAGGRGPASPVLFALMRLES LCH
 LCLACLFRLPATRTVYCMNEAEIVDVALGILIESRKQXKACEQPALAGADNP
 EHSPPCSVSPHTSSGSSSEEDSGKQALXPGLSPSQRPGGSSSACSRSPEEEE

- 5 EEDVLKYVREIFFS (SEQ ID NO: 204) . Polynucleotides encoding these polypeptides are also provided. Polynucleotides of the invention do not consist of the nucleic acid sequences shown as GeneSeq Accession Nos: V59595 and V59744, which are hereby incorporated herein by reference.

10 This gene is expressed primarily in a variety of immune cell types, including stromal cells, dendritic cells, leukocytes, activated T-cells, macrophages, monocytes, neutrophils and to a lesser extent in a variety of other adult and fetal tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer and other proliferative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

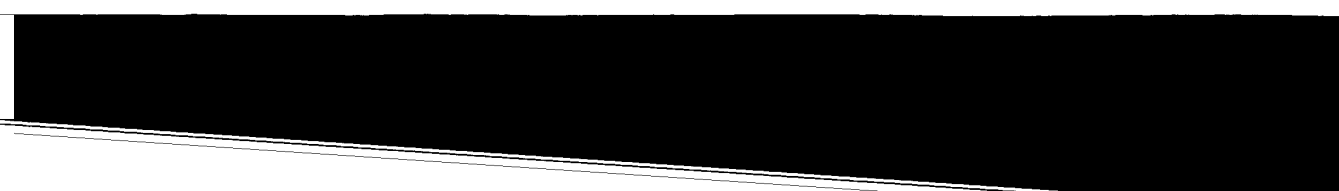
25 The tissue distribution in immune cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Expression of this gene product in fetal tissue and various hematopoietic cancers indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all

30

hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses).

5 Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory
10 bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, scleroderma and tissues. Moreover, the protein may represent a secreted
15 factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity,
20 raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

 Many polynucleotide sequences, such as EST sequences, are publicly
25 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
30 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1489 of SEQ ID NO:17, b is an



integer of 15 to 1503, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 8

5 When tested against Jurkat T-cell lines, supernatants removed from cells containing this gene activated the NF- κ B (Nuclear Factor κ B) pathway. Thus, it is likely that this gene activates T-cells through the NF- κ B signal transduction pathway. NF- κ B is a transcription factor activated by a wide variety of agents, leading to cell

10 promoter element are used to screen supernatants for such activity. Preferred polypeptides of the invention comprise the following amino acid sequence: VPGWPRACSPCQADSPRAHPPKLRGILRWAPVPLXCAALCPPLDSG MSMAACPEAPEPSFLREVPS SPASTQWHRPCNFRQVEANPRKEPKNLVWRD VSLGQXSRTPRGSGLELVRVCGGGMQRDKTVVEERVGEERERERERESLGG
15 AGKHGEMRCVYVRESVGAPGRAGGGGNGVNSVGCVRTVHSGSXPPPSAGV S (SEQ ID NO: 205). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in parts of the brain such as cerebellum and frontal lobe.

Therefore, polynucleotides and polypeptides of the invention are useful as
20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of
25 the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene
30 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in cerebellum and frontal lobe indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, prevention and/or treatment of neurodegenerative disease states and behavioural disorders, or inflammatory conditions. Representative uses are described

5 in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's

10 Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms,

hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the

15 brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to

20 identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

25 related to SEQ ID NO:18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

30 formula of a-b, where a is any integer between 1 to 1498 of SEQ ID NO:18, b is an

integer of 15 to 1512, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 9

5 In a specific embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

TRPGKELNLVFGQLQSMARIGSTVNMNLMGWLYSKIEALLGSAGHTTLGITL
 10 MIGGITCILSLICALALAYLDQRAERILHKEQGKTGEVIKLTVDKDFSLPLWLIF
 IICVCYYVAVFPFIGLGKVFFTEKFGFSSQAASAINSVVYVISAPMSPVFGLLV
 DKTGKNIIWVLCA (SEQ ID NO: 206). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome
 15 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

This gene is expressed primarily in fetal tissue, and to a lesser extent in a variety of adult human tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as
 20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, fetal abnormalities, particularly developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For
 25 a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., developing, or cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having
 30 such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 111 as residues: Lys-30 to Thr-35. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in fetal tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Furthermore, the protein

may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1641 of SEQ ID NO:19, b is an integer of 15 to 1655, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 10

The translation product of this gene shares sequence homology with human histiocyte-secreted factor (HSF) which is a novel cytokine that shows in vivo antitumour activity without the cytotoxicity associated with tumour necrosis factor. Furthermore, The translation product of this gene also shares sequence homology with the human endogenous virus S71 gag polyprotein, the sequence of which is believed to represent a transformation locus for several cancers (See Genebank Accession No. pir|A46312|A46312; all references available through this accession are hereby incorporated by reference herein). Similarly, The translation product of this gene also shares homology with B219, a sequence that is expressed in at least four isoforms in very primitive hematopoietic cell populations which may represent a novel hemopoietin receptor (See, e.g., Cioffi, et al. Nat. Med. 2:585-589 (1996), which is hereby incorporated by reference herein). In a preferred embodiment polypeptides of the invention comprise the following amino acid sequence:

CKDLCSR-VYLL-TLSPLLSYDPATSHSPRNTQ (SEQ ID NO: 207) . Also preferred are the polynucleotides encoding these polypeptides.

This gene is expressed primarily in tonsil, and colon, and to a lesser extent in a wide variety of human tissues.

5 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, hematopoietic, and gastrointestinal disorders, particularly

10 these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic, digestive and immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, gastrointestinal, or
15 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 112 as residues: Met-1 to Cys-6. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in tonsil and colon, combined with the homology to human histiocyte growth factor, the human endogenous viral protein, and B219
25 strongly indicate that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment and/or prevention, of a variety of hematopoietic and immune system disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19,
30 20, and 27, and elsewhere herein. Expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation

of potentially-all-hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses).

- 5 Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.
- 10
15
20

- Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2511 of SEQ ID NO:20, b is an
- 25
30

integer of 15 to 2525, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 11

5 The gene encoding the disclosed cDNA is believed to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

10 IICECWEEECQSCRLKITQPREICRMDFLVFLFYLASVLMGLVLICVCSKTHS
LKGLARGGAQIFSCIPECLQRAXHGLLHYLFHTRNHTFIVLHLVLQGMVYTE
YTWEVFGYCQELELSLHYLLPYLLLGVNLFFFTLTCGTNPGIITKANELLFLH
15 VYEFDEVMFPPKNVRCSTCDLRKPARSKHCSVCNWCVHRFDHHCVVWNCCI
GAWNIRYFLIYVLTLTASAATVAIVSTTFLVHLVVMSDLYQETYIDDLGHLHV
MDTVFLIQYLFLTFFPRIVFMLGFVVVLSFLLGGYLLFVLYLAATNQTNEWYR
GDWAWCQRCPLVAWPPSAEPQVHRNIHSHGLRSNLQEIFLPAFPCHERKKQE
(SEQ ID NO: 208). Polynucleotides encoding these polypeptides are also provided.

20 This gene is expressed primarily in colon and brain and to some extent in all tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological and digestive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and digestive system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neurological, gastrointestinal, 30 or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,

synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5 The tissue distribution in brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions.

Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly,
10 the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive
15 compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation,
20 neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Alternatively, expression of this gene in colon may indicate a role in the detection, prevention and/or treatment of colon disorders such as colon cancer, Crohn's Disease, ulcers, and digestive tract disorders in general. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to
25 isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
30 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:21 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
5 formula of a-b, where a is any integer between 1 to 1382 of SEQ ID NO:21, b is an integer of 15 to 1396, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 12

10 When tested against Reh cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activation site) pathway. Thus, it is likely that this gene activates B-cells through the Jaks-STAT signal transduction pathway. GAS is a promoter element found upstream in many genes which are involved in the Jaks-STAT pathway. The Jaks-STAT pathway is a large, signal
15 transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. This gene maps to chromosome 7, and therefore, is used as a marker in linkage analysis for chromosome 7.

20 This gene is expressed primarily in brain, and in the developing embryo.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, behavioral, immune, and developmental disorders.

25 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous and developmental systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural,
30 developing, immune, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue

or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 114 as residues: Lys-60 to Asn-67. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions.

Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the tissue distribution in developing embryo indicates that the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Alternatively, the biological activity within B-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Activation of genes within B-cells indicates a role for this protein in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses).

~~Since the gene is expressed in cells of lymphoid origin, the natural gene~~
product is involved in immune functions. Therefore it is also used as an agent for
immunological disorders including arthritis, asthma, immune deficiency diseases such
as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne,
5 and psoriasis. Furthermore, the protein may also be used to determine biological
activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors,
to identify agents that modulate their interactions; in addition to its use as a nutritional
supplement. Protein, as well as, ~~antibodies directed against the protein may show~~
utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

10 Many polynucleotide sequences, such as EST sequences, are publicly
available and accessible through sequence databases. Some of these sequences are
related to SEQ ID NO:22 and may have been publicly available prior to conception of
the present invention. Preferably, such related polynucleotides are specifically
excluded from the scope of the present invention. To list every related sequence is
15 cumbersome. Accordingly, preferably excluded from the present invention are one or
more polynucleotides comprising a nucleotide sequence described by the general
formula of a-b, where a is any integer between 1 to 1055 of SEQ ID NO:22, b is an
integer of 15 to 1069, where both a and b correspond to the positions of nucleotide
residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.

20

FEATURES OF PROTEIN ENCODED BY GENE NO: 13

The gene encoding the disclosed cDNA is believed to reside on chromosome
6. Accordingly, polynucleotides related to this invention are useful as a marker in
linkage analysis for chromosome 6.

25 In another embodiment, polypeptides comprising the amino acid sequence of
the open reading frame upstream of the predicted signal peptide are contemplated by
the present invention. Specifically, polypeptides of the invention comprise the
following amino acid sequence:

LLSFKIRGLRTEDAGWAQSSGGLCVRGDAFWMPSSSSGLGSPSRPPSSFLCL
30 LLLLPPAALALLFFLDFFPPRAAVSPFLPDHCSARQPRVWRRETLNRSASGL

GEWARSTEQGA VGVATGTVLDI SLPASCLSLWPPGPSGGI (SEQ ID NO: 209)

. Polynucleotides encoding these polypeptides are also provided.

In a specific embodiment polypeptides of the invention comprise the following amino acid sequence:

5 QLGLCLTSASLPPASRCGHQAPLGASDLSAHHSAPGFSDSYFTMSCQSSLSRA
EILQCPLVPSVSPPTHLPQGRANKSSRASLPLLPQTHWCLFPSARGWRRGIQSG
LPPGGSCTSPRSPQTLHQHITLVNHNTSYWQSPST (SEQ ID NO: 210) ,

HQPPCLLPLAVATRPLWGHLTCLPIHLVSVTLTSPCLANQAFQGQRSYNAL
WCPLFLLLPTSPKGEQTNHPEPACPCFPKLTGVFSLQHVVGAEFSQVFLLD
10 PVPVLDHLLKLFTSTSHLLIIPHIGKAPAPDSLL EELSLSLATHCKVAVARFT
(SEQ ID NO: 211) . Also preferred are the polynucleotides encoding these
polypeptides. Polynucleotides of the invention do not consist of the nucleic acid
sequence shown as GeneSeq Accession No. X04377, which is hereby incorporated
herein by reference.

15 This gene is expressed primarily in brain.

Therefore, polynucleotides and polypeptides of the invention are useful as
reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
not limited to, behavioral and neurological disorders. Similarly, polypeptides and
20 antibodies directed to these polypeptides are useful in providing immunological
probes for differential identification of the tissue(s) or cell type(s). For a number of
disorders of the above tissues or cells, particularly of the central nervous system,
expression of this gene at significantly higher or lower levels is routinely detected in
certain tissues or cell types (e.g., neural, or cancerous and wounded tissues) or bodily
25 fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another
tissue or cell sample taken from an individual having such a disorder, relative to the
standard gene expression level, i.e., the expression level in healthy tissue or bodily
fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic
30 epitopes shown in SEQ ID NO: 115 as residues: Pro-2 to Gly-7, Ser-10 to Ser-16,

Pro-52 to Val-62, Arg-64 to Ser-73. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:23 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1644 of SEQ ID NO:23, b is an

integer of 15 to 1658, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 14

5 The translation product of this gene was shown to have homology to the lysosomal mannosidase alpha-B protein (See Genebank Accession No. P34098) which is thought to be important in protein metabolism. One embodiment of this gene comprises polypeptides of the following amino-acid sequence:

MAAEGSRFSSQSPGLVDRQGPKCDPSRLVSPWGRHGLRILQIGHHHGRDQGH
10 EATHHLLRVLRAPRVGKADEGAVDSDPSTPLQLKHEAAHAEDHAQQVHVVR
RRVVQGRVTFARRGLVPQHFRPPWVRHIVSGHSESKARSRLFRCRNRSFRR
AS (SEQ ID NO: 212) , and/or

RLVSPWGRHGLRILQIGHHHGRDQGH EATHHLL RVLRA (SEQ ID NO: 213) .

An additional embodiment is the polynucleotides encoding these polypeptides. This
15 gene maps to chromosome 19, and therefore, is used as a marker in linkage analysis for chromosome 19.

This gene is expressed primarily in brain, placenta, fetal liver, and to a lesser extent in most tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as
20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, reproductive, and hepatic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For
25 a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, hepatic, or cancerous and wounded tissues) or bodily fluids (e.g., bile, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a
30 disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 116 as residues: Asn-34 to Lys-42, Leu-60 to Trp-70.

Polynucleotides encoding said polypeptides are also provided.

The tissue distribution predominantly in brain indicates a role in the
5 detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder.

Alternatively, the tissue distribution in liver indicates that polynucleotides and
10 polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g., hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma.

15 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:24 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
20 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1063 of SEQ ID NO:24, b is an integer of 15 to 1077, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.

25

FEATURES OF PROTEIN ENCODED BY GENE NO: 15

This gene is expressed primarily in spinal cord, Merkel cells, and adipose tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as
30 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, disorders of the nervous and immune systems, particularly those disorders relating to the CNS involving lipid metabolism disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For

5 a number of disorders of the above tissues or cells, particularly of the nervous and immune systems and adipose tissue, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, immune, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an

10 individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in spinal cord, Merkel cells and adipose tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the

15 treatment and/or diagnosis of diseases the nervous systems, such as spinal cord injury, neurodegenerative diseases, muscular dystrophy or obesity. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly

20 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:25 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

25 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1191 of SEQ ID NO:25, b is an integer of 15 to 1205, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.

30 **FEATURES OF PROTEIN ENCODED BY GENE NO: 16**

The translation product of this gene shares sequence homology with the human uncoupling protein-2 which is thought to be important in energy metabolism, obesity, and the predisposition of hyperinsulinemia (See Genebank Accession No. gi|1857278). Recently, another group published on this gene, designating it brain mitochondrial carrier protein-1 (BCMP1) (J Biol Chem 1998 Dec 18;273(51):34611-5). One embodiment of this gene comprises polypeptides of the following amino acid sequence: PTDVLKIRMQAQ (SEQ ID NO: 214) , and/or TYEQLKR (SEQ ID NO: 215) . An additional embodiment is the polynucleotides encoding these polypeptides. This gene maps to the X chromosome, and therefore, is used as a marker in linkage analysis for the X chromosome.

This gene is expressed primarily in manic depression brain tissue, epileptic frontal cortex, human erythroleukemia cell line, T-helper cells, and to a lesser extent in endothelial and amygdala cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the central nervous system or hematopoietic/immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system or hematopoietic/immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, hemolymphoid, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 118 as residues: Ser-34 to Thr-39, Gln-198 to Leu-205. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution-in-neural-tissues combined with the homology to the human uncoupling protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and/or treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and preception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Alternatively, given the homology to uncoupling proteins, the gene and/or its translation product may also be used in the diagnosis, treatment, and/or prevention of thermogenesis disorders such as obesity, cachexia, and hyperinsulinemia. Uncoupling proteins dissipate the proton gradient created from the oxidation of fuels by the electron transport chain, thus releasing stored energy as heat. Dysfunction of thermogenesis can induce disorders such as obesity and cachexia. It is thought that obesity may result from decreased thermogenesis in humans. Alternatively, cachexia is a metabolic state in which energy expenditure exceeds food intake, for example in anorexia nervosa. Uncoupling proteins is useful for the treatment and/or prevention of diseases and/or disorders involved with aberrant metabolic and thermogenic pathways. The following method provides for the determination of respiration uncoupling activity of the polypeptides of the present invention, including fragments and variants of the full length proteins.

Briefly, yeast are transfected with an expression vector expressing polypeptide of the present invention as previously described by Bouillaud et al., EMBO J., 13:1990 (1994) (incorporated by reference herein in its entirety). Rates of growth in liquid medium of transformed yeast are measured in the presence of galactose, which induces expression, as described in International Publication No. WO 98/31396

(incorporated by reference herein in its entirety). Instantaneous generation times are compared between the polypeptide of the present invention and appropriate controls.

An in vivo decrease of membrane potential associated with uncoupling of respiration is analyzed by flow cytometry of yeast labeled with the potential sensitive probe

- 5 DiOC6 (3) (3,3'-dihexyloxacarbocyanine iodine, Molecular Probes, Eugene, OR). The ability of a polypeptide of the present invention to influence mitochondrial activity and uncouple respiration is thus determined.

- Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
- 10 related to SEQ ID NO:26 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
- 15 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1660 of SEQ ID NO:26, b is an integer of 15 to 1674, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 17

- 20 The translation product of this gene shares sequence homology with 55 kD deglycosylated zona pellucida protein which is known to be important in egg fertilization (See Genebank Accession No.R39356). Preferred polypeptides of the invention comprise the following amino acid sequence:

- 25 RPRPSASSLARSASLLPAAHGXGVGGAGGGSSXLRORYQQQLQNEEESGEPEQ
AAGDAPPPYSSISAESAHXFDYKDESGFPKPPSYNVATTLPSYDEAERTKAEA
TIPLVPGRDEDFVGRDDFDDADQLRIGNDGIF (SEQ ID NO: 216) ,
RYQQQLQNEEESGEPEQAAGD (SEQ ID NO: 217) , and/or
PGRDEDFVGRDDFDDADQLRIG (SEQ ID NO: 218) . Polynucleotides encoding
30 these polypeptides are also provided.

Preferred polypeptide fragments of the invention comprise the following amino acid sequence: MLTFFMAFLFNWIGFFLSFCLTTSAAGRYG

AISGFGLSLIKWILIVRFSTYFPGYFDGQY

WLWWVFLVLGFLFLRGFINYAKVRKMPET FSNLPRTRVLFYI (SEQ ID NO:

- 5 219). Polynucleotides encoding these polypeptides are also provided.

Preferred polypeptide variants of the invention comprise the following amino

acid sequence:

MKKSLENLNLRLQVMLLHLTAAFLQRAQHXYFDYKDESGFPKPPSYNVATTLPS

YDEAERTKAEATIPLVGRDEDFVGRDDFDDADQLRIGNDGIFMLTFFMAFLF

- 10 NWIGFFLSFCLTTSAAGRYGAISGFGLSLIKWILIVRFSTYFPGYFDGQYWLW

WVFLVLGFLFLRGFINYAKVR KMPETFSNLPRTRVLFYI (SEQ ID NO: 220),

MLLHLTAAFLQRAQFSTYFPGYFDGQYWLWWVFLVLGFLFLRGFINYAKV

RKMPETFSN LPRTRVLFYI (SEQ ID NO: 221), MLTFFMAFLFNWIGFFLSFCLT

TSAAGRYGAISGFGLSLIKWILIVRFSTYFPAFMNSLSRSKRTPAGSESRCRTQ

- 15 RNNHLL (SEQ ID NO: 222), and/or

MKKSLENLNLRLQVMLLHLTAAFLQRAHXIL TTRMSLGFQSPHLTM (SEQ ID

NO: 223) . Polynucleotides encoding these polypeptides are also provided.

When tested against U937 cell lines, supernatants removed from cells

containing this gene activated the GAS (gamma activating sequence) promoter

- 20 element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent,

other immune and hematopoietic cells and JAK-STAT signal transduction pathway.

GAS is a promoter element found upstream of many genes which are involved in the

Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway

involved in the differentiation and proliferation of cells. Therefore, activation of the

- 25 Jak-STAT pathway, reflected by the binding of the GAS element, can be used to

indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in adult kidney, colon adenocarcinoma, and

fetal brain, and to a lesser extent, ubiquitously expression in many tissues.

- 30 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, disorders of kidney, colon cancers, and central nervous system.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the
5 renal and neural systems, and cancers, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., renal, neural, urogenital, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken
10 from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 119 as residues: Cys-15 to Gly-36. Polynucleotides encoding said polypeptides are also provided.

15 The tissue distribution adult kidney, colon adenocarcinoma, and fetal brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of kidney diseases, colon cancers, and disorders of the central nervous system. Additionally, the homology to the zona pellucida protein indicates that the gene product is used for male contraceptive development, and
20 infertility diagnosis etc. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
25 related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
30 formula of a-b, where a is any integer between 1 to 1951 of SEQ ID NO:27, b is an

integer of 15 to 1965, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 18

5 The translation product of this gene shares sequence homology with the chicken transferrin receptor in addition to a human prostate-specific protein homolog (See Genbank Accession Nos. [pir|JH0570|JH0570](#) and [gi|2565338 \(AF026380\)](#), respectively). This gene also shares significant homology with both the murine and the rat hematopoietic lineage switch 2 proteins (See Genbank Accession Nos. [g3169729](#) and [g3851632](#), respectively), which are induced during an erythroid to myeloid lineage switch.

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: **MTVMDPKQMNVA AAVWAVVSYVVADMEEML PRS** (SEQ ID NO: 224). Polynucleotides encoding these polypeptides are also provided.

15 This gene is expressed primarily in fetal tissues, such as liver/spleen and brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pre-natal disorders, anomalies, deficiencies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing fetus, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., developing, cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 120 as residues: Arg-31 to Lys-37, Lys-58 to Glu-65,

Asp-157 to Gly-168, Ile-219 to Gly-225, Ala-260 to Ser-268, Thr-276 to Glu-282.

Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of pre-natal disorders, anomalies and deficiencies. The homology to the hematopoietic lineage switch 2 proteins indicates that The translation product of this gene is useful for the detection and/or treatment of immune system disorders. In addition, the homology to the transferrin receptor indicates that the translation product of the present invention may have utility in the regulation of iron metabolism as well as the numerous genes under the stringent control of physiologic iron levels. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1849 of SEQ ID NO:28, b is an integer of 15 to 1863, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 19

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

PRVRSREPVAGAPGCGTAGPPAMATLWGGLRLGSLLSLCLALSLLLLAHC
QTPPSDCLHVVEPMPVVRGPDVEAYCLRCECKYEERSSVTIKVTHIYLSILGLLL
LYMVYLTLEPILKRRLFGHAQLIQSDDDIGDHQPFANAHDVLARSRSRANV

LNKVEYAQQRWKLQVQEQRKSVFDRHVVLS (SEQ ID NO: 225).

Polynucleotides encoding these polypeptides are also provided.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 72 - 88 of the amino acid sequence referenced in
5 Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 89 to 167 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

A preferred polypeptide variant of the invention comprise the following amino
10 acid sequence:

MATLWGGLRLGSLLSLSCLALSVLLLAHCQTPPRISMSDVNVSALPIKKNS
GHIYNKNISQKDCDCLHVVEPMPVRGPDVEAYCLRCECKYEERSSVTIKVTIII
YLSILGLLLLYMVYLTLEPILKRRLFGHAQLIQSDDDIGDHQPFAHAHDVLA
RSRSRANVLNKVEYGTAALEASSPRAAKSLSLTGMLSSANWGIEFKVTRKKQ
15 ADNWKGTDWVLLGFILIPC (SEQ ID NO: 226). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in infant brain tissue, and to a lesser extent in other cell types and tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as
20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental and neurodegenerative diseases of the brain and nervous system, such as depression, schizophrenia, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, mania, dementia, paranoia, addictive behavior, sleep
25 disorders, epilepsy, transmissible spongiform encephalopathy (TSE), Creutzfeldt-Jakob disease (CJD). Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher
30 or lower levels is routinely detected in certain tissues or cell types (e.g., neural, developmental, or cancerous and wounded tissues) or bodily fluids (e.g., amniotic

fluid, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 121 as residues: Gln-110 to Pro-120, Val-152 to Val-159. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in infant brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis
10 of developmental, degenerative and behavioral conditions of the brain and nervous system. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of schizophrenia, Alzheimer's Disease, Parkinson's
15 Disease, Huntington's Disease, Tourette Syndrome, transmissible spongiform encephalopathy (TSE), Creutzfeldt-Jakob disease (CJD), mania, depression, dementia, paranoia, addictive behavior, obsessive-compulsive disorder and sleep disorders. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to
20 identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
25 related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
30 formula of a-b, where a is any integer between 1 to 1612 of SEQ ID NO:29, b is an

integer of 15 to 1626, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 20

- 5 The translation product of this gene shares sequence homology with a recently published gene Dysferlin, which is thought to be a skeletal muscle gene that is mutated in Miyoshi myopathy and limb girdle muscular dystrophy (See Genbank Accession No. g3600028, and Nat. Genet. 20 (1), 31-36 (1998)).

This gene is expressed primarily in fetal liver, fetal heart tissue, and T-cells.

- 10 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunodeficiency, tumor necrosis, lymphomas, auto-immunities, cancer, inflammation, anemias (leukemia) and liver disorders, vascular disorders, and
- 15 cancers (e.g., hepatoblastoma, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver and
- 20 immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., hepatic, developmental, vascular, or cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, bile, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard
- 25 gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune disorders including: leukemias, lymphomas, auto-immunities, immunodeficiencies
- 30 (e.g., AIDS), immuno-suppressive conditions (transplantation) and hematopoietic disorders. In addition this gene product is applicable in conditions of general

microbial infection, inflammation or cancer. Expression in liver may suggest a role for this gene product in the treatment and detection of liver disorders and cancers (e.g., hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Alternatively, the tissue distribution in fetal heart tissue indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular system, such as heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis, and wound healing. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Additionally, the homology to the dysferlin gene indicates that polynucleotides and polypeptides corresponding to this gene are useful for diseases related to degenerative myopathies that are characterized by the weakness and atrophy of muscles without neural degradation; such as Duchenne and Becker's muscular dystrophies. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 591 of SEQ ID NO:30, b is an integer of 15 to 605, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 21

This gene is expressed primarily in haemopoietic cells and tumor cells, such as pancreatic tumor tissue, and to a lesser extent in bladder cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, haemopoietic disorders, diseases of the renal and pancreatic systems, and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemopoietic, pancreatic, and renal systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., pancreas, renal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of disorders of the renal, pancreatic and haemopoietic systems, and cancers thereof. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 917 of SEQ ID NO:31, b is an integer of 15 to 931, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 22

This gene is expressed primarily in liver tissue, cancer cells and fetal lung tissue, and to a lesser extent in dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic disorders, diseases of developing systems and cancers.

Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetus, metabolic systems and cancers, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., developing, metabolic, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 124 as residues: His-44 to Gly-49. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of disorders of the fetus, metabolic systems and cancers. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:32 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1393 of SEQ ID NO:32, b is an integer of 15 to 1407, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 23

This gene is expressed primarily in central nervous system tissues and cancers, such as endometrial tumors, and to a lesser extent in other tissues and organs.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the CNS and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and cancerous tissues, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 125 as residues: Tyr-16 to Ser-22, Asp-209 to Leu-215. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in central nervous system tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of diseases of the central nervous system, as well as cancers of tissues where expression of this gene has been observed, such as in
5 endometrial tumors. The tissue distribution in central nervous system tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease,
Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive
10 disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein
15 may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:33 and may have been publicly available prior to conception of
20 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1512 of SEQ ID NO:33, b is an
25 integer of 15 to 1526, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 24

The translation product of this gene shares sequence homology with low-
30 density lipoprotein receptor (See Genbank Accession No. >dbj|BAA24580.1), which is thought to be important in the pathogenesis of atherosclerosis and other disorders.

The translation-product of this gene also shares sequence homology with a rat homolog of the human CD94 (See Genbank Accession No. gb|AAC10220.1).

This gene is expressed primarily in macrophages, eosinophils, neutrophil and other cells of the haemopoietic and immune system.

5 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the immune and haemopoietic systems and diseases of the endothelial and vascular system. Similarly, polypeptides and antibodies directed to
10 these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, haemopoietic and vascular system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily
15 fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic
20 epitopes shown in SEQ ID NO: 126 as residues: Lys-9 to Ala-17, Met-55 to Leu-61, Tyr-105 to Cys-127, Asp-132 to Lys-141, Ser-165 to Tyr-172, Pro-178 to Met-186, His-222 to Gln-227. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution and homology to LDL receptor and rat CD94 homolog indicates that polynucleotides and polypeptides corresponding to this gene are useful
25 for the treatment and/or diagnosis of disorders of the immune, haemopoietic and vascular systems. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or
30 differentiation of hematopoietic lineages. Expression of this gene product in eosinophils and macrophage also strongly indicates a role for this protein in immune

function-and-immune-surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
 5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
 10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1723 of SEQ ID NO:34, b is an integer of 15 to 1737, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.

15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 25**

A preferred polypeptide fragment of the invention comprises the following amino acid sequence:

MAAAGRLPSSWALFSPLLAGLALLGVGPVPARALHNVTAELFGAEAWGTLA
 AFGDLNSDKQTDLFVLRERNDLIVFLADQNAPYFKPKVKVSFKNHSALITSVV
 20 PGDYDGDSQMDVLLTYLPKNYAKSELGAVIFWGQNQTLDPNMTILNRTFQ
 DEPLIMDFNGDLIPDIFGITNESNQPIQLGGLNSWHPALTTTSKMRIPHSHAFI
 DLTEDFTADLFLTTLNATTSTFQFEIWENLDGNFSVSTILEKPQNMVVGQSA
 FADFDGDGHMDHLLPGCEDKNCQKSTIYLVRSGMKQWVPVLQDFSNGKTL
 WGFVPFVDEQQPTEIPIPTLHIGDYNMDGYPDALVILKNTSGSNQQAFLLENV
 25 PCNNASCEEARRMFKVYWELTDLNQIKDAMVATFFDIYEDGILDIVVLSKGY
 TKNDFAIHTLKNNFEADAYFVKVIVLSGLCS NDCPRR (SEQ ID NO: 227).

Polynucleotides encoding these polypeptides are also provided.

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter
 30 element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, other immune and hematopoietic cells and tissue cell types, through the JAK-STAT

signal-transduction-pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the
5 GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in infant brain and placental tissues, and to a lesser extent in several other tissues including cancers.

Therefore, polynucleotides and polypeptides of the invention are useful as
10 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, brain disorders and diseases of developing systems and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell
15 type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and fetal systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken
20 from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 127 as residues: Leu-56 to Thr-62, Gln-80 to Pro-87,
25 Gly-106 to Gln-113, Pro-122 to Lys-127, Gln-138 to Asn-146. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in neural tissues and developing tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of disorders of the central nervous system, disorders of
30 developing systems, and cancers. The tissue distribution in infant brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful

for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product is produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product is produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of $a-b$, where a is any integer between 1 to 2228 of SEQ ID NO:35, b is an integer of 15 to 2242, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to $a + 14$.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 26

Preferred polypeptides of the invention comprise the following amino acid sequence:

MTKREDGGYTFTATPEDFPKKHKAPVIDIGIANTGKFIMTASSDITTVLIWSLK
 GQVLSTINTNQMNNTAAVSPCGRFVASCFTPDKVWEVCFGKKGEFQEV
 10 VRA FELKGHSA AVHSFAFSNDSRRMASVSKDGTWKLWDTXVEYKKKQDPY
 LLKTGRFEEAAGAXPCRLALSPNAQVLALASGSSIHLYNTRRGEKEECFERVH
 GECIANLSFDITGRFLASCGDRAVRLFHNTPGHRAMVEEMQGH LKRASNEST
 RQRLQQQLTQAQETLKS LGALKK (SEQ ID NO: 228). Polynucleotides encoding
 such polypeptides are also provided.

15 The gene encoding the disclosed cDNA is thought to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates
 20 myeloid cells through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS
 25 element, can be used to indicate proteins involved in the proliferation and differentiation of cells. Recently, another group published this gene, naming it WS beta-transducin repeats protein (See Human Genetics 103 (5), 590-599 (1998); which is hereby incorporated herein by reference), in which it was suggested that the protein is involved in William's Disease.

30 The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 12 - 28 of the amino acid sequence referenced in

Table I for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ib membrane proteins.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the
5 following amino acid sequence:

VIRHEGSTNMELSQMSXLMGLSVLLGLLALMATAAVXRGWLRAGEERSGRP
ACQKANGFPDKSSGSKKQKQYQIRKEKPQHNETHRLAAALKSHSGNIS
CMDFSSNGKYLATCADDRTIRIWSTKDFLQREHRSMRANVELDHATLVRFP
10 DCRAFIVWLANGDTLRVFKMTKREDGGYTFTATPEDFPKKHKAPVIDIGIAN
TGK
FIMTASSDTTVLIWSLKGQVLSTINTNQMNNTAAVSPCGRFVASCGFTPDVK
VWEVCFGKKGEFQEVVRAFELKGHSAAVHSFAFSNDSRRMASVSKDGTWK
LWDTXVEYKKKQDPYLLKTGRFEEAAGAXPCRLALSPNAQVLALASGSSIHL
15 YNTRRGEKEECFERVHGECIANLSFDITGRFLASCGDRAVRLFHNTPGHRAM
VEEMQGHKLRASNESTRQLQQQLTQAQETLKS LGALKK (SEQ ID NO: 229).
Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in testes, synovial sarcoma and fetal tissues, and to a lesser extent in several other tissues.

20 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the reproductive and developing systems and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in
25 providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and developing systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, testicular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum,
30 plasma, seminal fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in testes tissue, synovial sarcoma, and fetal tissues, indicates that polynucleotides and polypeptides corresponding to this gene are useful
5 for the treatment and/or diagnosis of disorders of the reproductive and developing systems, and cancers. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm
10 maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene
15 expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.

Furthermore, the tissue distribution indicates that polynucleotides and
20 polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the
25 proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene is useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in
30 pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. This protein is useful for

the treatment, detection, and/or prevention of William's Disease. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:36 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2221 of SEQ ID NO:36, b is an integer of 15 to 2235, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 27

Preferred polypeptides of the invention comprise the following amino acid sequence positions 1-363, 2-363, 4-363, 5-363, 30-363, 31-363, 32-363, 75-363, 76-363 and 82-363 of the following amino acid sequence:

MSVMVVRKKVTRKWEKLPGRNTFCCDGRVMMARQKGIFYLTLFLILGTCTL
FFAFECRYLAVQLSPAIPVFAAMLFLFSMATLLRTSFSDPGVIPRALPDEAAFIE
MEIEATNGAVPQGQRPPRIKNFQINNQIVKLKYCYTCKIFRPPRASHCSICDN
CVERFDHHCPWVGNCVGKRNRYRYFYLFILSLSLLTIYVFAFNIVYVALKSLKI
GFLETLKETPGTVLEVLCFFTLWSVVGLTGFHTFLVALNQTTNEDIKGSWTG
KNRVQNPYSHGNIVKNCCEVLCCGPLPPSVLDRRGILPLEESGRPPSTQETSSS
LLPQSPAPTEL NSNEMPEDSSTPEEMPPPEPPEPPQEA AEAEK (SEQ ID NO:
230). Polynucleotides encoding such polypeptides are also provided.

A preferred polypeptide variant of the invention comprises the following amino acid sequence: MLFLFSMATLLRTSFSDPGVIPRALPDEAA

FIEMEIEATNGA-VPQGQRPPRIKNFQINNQIVKLKCYTCKIFRPPRASHCSIC
 DNCVE RFDHHCPWVGNCVGKRNRYFYFLFILSLSLTIYVFAFNIVYVALK
 SLKIGFLETLKGNS WNCSRSPHLLLYTLVRRGTDWISYFPRGSQ PDNQ (SEQ
 ID NO: 231). Polynucleotides encoding these polypeptides are also provided.

- 5 This gene is expressed primarily in ovarian and endometrial tumors, fetal liver, spleen and brain tissues, and to a lesser extent in several other tissues and organs.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the developing systems, and cancers of the female reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing, female reproductive and fetal systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.
- 10 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the developing systems, and cancers of the female reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above
- 15 tissues or cells, particularly of the developing, female reproductive and fetal systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a
- 20 disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 129 as residues: Pro-44 to Lys-54, Cys-88 to His-95, Val-103 to Tyr-108, Gln-181 to Ser-190, Thr-192 to Ile-206, Glu-233 to Ser-245, Ser-252 to Ala-286. Polynucleotides encoding said polypeptides are also provided.
- 25 252 to Ala-286. Polynucleotides encoding said polypeptides are also provided.

- The tissue distribution in developing systems indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of disorders of developing and fetal systems, and cancers. Furthermore, the tissue distribution in ovarian and endometrial tumor tissues indicates that the translation product of this gene is useful for the detection, diagnosis, and/or treatment of cancers of the female reproductive system. Accordingly, preferred are antibodies
- 30 translation product of this gene is useful for the detection, diagnosis, and/or treatment of cancers of the female reproductive system. Accordingly, preferred are antibodies

which specifically bind a portion of ~~The translation product of this gene.~~ Also provided is a kit for detecting these tumors. Such a kit comprises in one embodiment an antibody specific for ~~The translation product of this gene bound to a solid support.~~ Also provided is a method of detecting these tumors in an individual which
5 comprises a step of contacting an antibody specific for ~~The translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum.~~ The above
10 embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
15 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2957 of SEQ ID NO:37, b is an integer of 15 to 2971, where both a and b correspond to the positions of nucleotide
20 residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 28

This gene is expressed primarily in normal and cancerous colon tissue, macrophages, endothelial cells and placental tissue, and to a lesser extent in several
25 other tissues and organs.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, colon cancer and gastrointestinal disorders, immune disorders, vascular
30 diseases and disorders of developing systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for

differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, vascular and developing systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, gastrointestinal, developmental, vascular, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 130 as residues: Thr-27 to Ser-33. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in macrophage, endothelial and placental tissues, and normal and cancerous colon tissues, indicates that polynucleotides and polypeptides
15 corresponding to this gene are useful for the treatment and/or diagnosis of immune, gastrointestinal and vascular disorders and diseases. Expression of this gene product in colon tissue indicates involvement in digestion, processing, and elimination of food, as well as a potential role for this gene as a diagnostic marker or causative agent in the development of colon cancer, and cancer in general. Accordingly, preferred are
20 antibodies which specifically bind a portion of the translation product of this gene. Also provided is a kit for detecting colon cancer. Such a kit comprises in one embodiment an antibody specific for The translation product of this gene bound to a solid support. Also provided is a method of detecting colon cancer in an individual which comprises a step of contacting an antibody specific for The translation
25 product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein. Alternatively, the tissue
30 distribution in placental tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders

of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product is produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta and endothelial cells also indicates that this gene product is produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Additionally, expression of this gene product in macrophage also strongly indicates a role for this protein in immune function and immune surveillance. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1149 of SEQ ID NO:38, b is an integer of 15 to 1163, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 29

The translation product of this gene shares homology with HNK-sulfotransferase, which directs glycan synthesis (see Genbank Accession no. AF033827).

This gene is expressed primarily in activated T cells, osteoclastoma, and glioblastoma, and to a lesser extent in various other normal and transformed cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation, immune defects, cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hemopoietic systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 131 as residues: Pro-32 to Gly-48, Gln-63 to Thr-69, Pro-77 to Trp-84, Val-88 to Leu-94. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in T-cells and various types of neoplasms indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, study and/or treatment of inflammatory and general immune defects, and various types of neoplasms. Expression of this gene product in T cells strongly indicates a role for this protein in immune function and immune surveillance. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the tissue distribution in various cancerous tissues indicates that the translation product of the gene is useful for the detection, diagnosis, and/or treatment of these cancers, as well as cancers of other tissues where expression has been observed. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1918 of SEQ ID NO:39, b is an integer of 15 to 1932, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 30

Preferred polypeptides of the invention comprise the following amino acid sequence:

- 5 LHECLPGSISYLHPRTPWLCCLPPQHLSFSTFSPPWQPAMSPVPGTGGPPCGL
(SEQ ID NO: 232), and/or
MLPLLIICLLPAIEGKNCLRCWPELSALIDYDLQILWVTPGPPTELSQSIHSLFLE
DNNFLKPWYLDRDHLEETAKFFTQVHQAIKTLRDDKTVLLEEIYTHKNLFT
ERLNKISDGLKEKGAPPLHECLPGSISYLHPRTPWLCCLPPQHLSFSTFSPPWQP
10 AMSPVPGTGGPPCGL (SEQ ID NO: 233). Polynucleotides encoding these
polypeptides are also provided.

This gene is expressed primarily in infant brain, testes and activated T cells, and to a lesser extent in various other normal and transformed cell types.

- Therefore, polynucleotides and polypeptides of the invention are useful as
15 reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
not limited to, neurological, reproductive and inflammatory conditions. Similarly,
polypeptides and antibodies directed to these polypeptides are useful in providing
immunological probes for differential identification of the tissue(s) or cell type(s). For
20 a number of disorders of the above tissues or cells, particularly of the neural, immune
and male reproductive systems, expression of this gene at significantly higher or
lower levels is routinely detected in certain tissues or cell types (e.g., neural, immune,
reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum,
plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken
25 from an individual having such a disorder, relative to the standard gene expression
level, i.e., the expression level in healthy tissue or bodily fluid from an individual not
having the disorder.

- Preferred polypeptides of the present invention comprise immunogenic
epitopes shown in SEQ ID NO: 132 as residues: Gly-41 to Leu-46, Asp-67 to Thr-75,
30 Ile-114 to Ala-123. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in infant brain tissue, testes tissue, and activated T-cells, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study, diagnosis, and/or treatment of neurological, reproductive and immune system disorders. Expression of this gene product in T-cells indicates a role
5 in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

10 Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it is also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease,
15 sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell type. Alternatively, the tissue distribution in testes tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions
20 concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis
25 of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.

30 Furthermore, the tissue distribution in infant brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the

detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 867 of SEQ ID NO:40, b is an integer of 15 to 881, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 31

The translation product of this gene shares sequence homology with some human and rodent melanoma and leukocyte specific antigens (see, for example, Genbank accession nos: gi|189384, gi|205898 and gi|180926). In addition, The translation product of this gene shares sequence homology with Tetraspan protein (see, for example, Genbank accession number: GI 3152703). Therefore, it is likely that the polypeptide of this gene shares some biological functions, such as cell-to-cell signaling, adhesion, proliferation, and differentiation with Tetraspan.

The polypeptide of this gene has been determined to have two transmembrane domains at about amino acid position 52-68 and 197 - 213 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed

that the protein product of this gene shares structural features to type IIIa membrane proteins.

The transmembrane 4 superfamily (TM4SF) or tetraspan superfamily has at least 16 members (including CD9, CD20, CD37, CD53, CD63, CD81, CD82, A15, 5 CO-029, Sm23, RDS, Uro B, Uro A, SAS, Rom-1, PETA3, and YKK8), is the second biggest subfamily among CD antigen superfamily. and activation antigen of T- cells. All TM4SF member contains four putative transmembrane domains, two extracellular loops, and two short cytoplasmic tails. They are variously expressed on Immature, 10 early, mature, activated lymphocytes, monocytes, macrophages, granulocytes, platelets, eosinophils, basophils, certain leukemic and lymphoma cells, and a variety of other cells and tissues. CD9 cell surface protein is expressed by both hematopoietic and neural cells, and may play a role for CD9 in intercellular signaling in the immune and nervous system. CD63 is a 53-Kd lysosomal membrane glycoprotein that has been identified as a platelet activation molecule, which play important role in cell 15 adhesion of platelets and endothelial cells. Increased mRNA for CD63 antigen was found in atherosclerotic lesions of Watanabe heritable hyperlipidemic rabbits, suggesting a potential role of CD63 in progression of atherosclerosis. CD63 is also a mast cell marker.

CD82 was originally identified as the target of several mAbs inhibitory to 20 syncytium formation induced by human T-cell leukemia virus type I (HTLV-I), the etiological agent of adult T-cell leukemia. Therefore, this gene could be a target for the development of a drug for this leukemia. CD81 is the target of an antiproliferative antibody. A diverse group of human cell lines, including hematolymphoid, neuroectodermal, and mesenchymal cells, express the CD81 protein. Many of the 25 lymphoid cell lines, in particular those derived from large cell lymphomas, were susceptible to the antiproliferative effects of the antibody. CD81 may therefore play an important role in the regulation of lymphoma cell growth. CD9, CD20, CD37, CD63, CD81 and CD82 have been implicated in the regulation of cell growth, adhesion, and signal transduction of B, T lymphocytes and some other non-lymphoid 30 cells. They associate with CD2, CD21, CD4, CD8, MHC Class II molecules, integrins, function as co-receptor for T, B and other lymphoid cells. Some

TM4SF are leukocyte antigens, highly expressed in activated leukocytes, lymphocytes, are highly specific surface marker for lymphoblastic leukemia, lymphoma, melanoma, and neuroblastoma. CD9 has been show to be involved in cell motility and tumor metastasis. These antigen could be a valuable immunogen or
5 target to implement active and passive immunotherapy in patients with cancer. Others have been shown to be involved in inhibition of prostate cancer metastasis. This gene has close homology to C33 antigen (CD82), which is a member of the transmembrane
4 superfamily (TMSF) and activation antigen of T- cells. C33 Ag (CD82 was originally identified as the target of several mAbs inhibitory to syncytium formation
10 induced by human T-cell leukemia virus type I (HTLV-I), the etiological agent of adult T-cell leukemia. Therefore, this gene could be very important target for developing drug for leukemia. Other members of this family are Sm23, CO-029, R2, TAPA-1, CD9, CD37, CD53, and CD63. CD63 is a 53-Kd lysosomal membrane glycoprotein that has been identified as a platelet activation molecule.

15 There is strong evidence indicating that CD63 and Pltgp40, a platelet membrane glycoprotein are the same molecule and that CD63/Pltgp40 is identical to the well-characterized, stage-specific melanoma-associated antigen ME491. These antigen could be valuable immunogens or target to implement active and passive immunotherapy in patients with cancer.

20 This gene is expressed primarily in fetal tissue (kidney, heart, liver, spleen, brain), macrophages, dendritic cells, retina and to a lesser extent in various other tissues, mostly of lymphoid origin or epithelial cell types. In addition This gene is expressed in cancerous tissues (e.g. breast).

Therefore, polynucleotides and polypeptides of the invention are useful as
25 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic diseases and/or disorders and cancers in a variety of organs and cell types. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential
30 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at

significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., developmental, proliferating, immune, hematopoietic, integumentary, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid, spinal fluid, or amniotic fluid) or another tissue or cell sample taken
5 from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 133 as residues: Tyr-123 to Tyr-131, Cys-134 to Ser-
10 145, Tyr-234 to Tyr-244. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution fetal cells and tissues and homology to tumor antigens indicates that polynucleotides and polypeptides corresponding to this gene are useful for study, treatment and diagnosis of lymphoid and epithelial disorders and
15 neoplasms. Additionally, tissue distribution in immune cells and other tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting hematopoiesis, including cancers. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere
20 herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

25 Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities,
30 such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity

disorders, such as autoimmune infertility, ~~lense-tissue injury~~, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits

5 hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of

10 cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern

15 formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of

20 potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types

25 of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new

30 insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue

markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ-ID NO:41 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
10 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1918 of SEQ ID NO:41, b is an integer of 15 to 1932, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 32

The translation product of this gene shares limited sequence homology with VEGF which is thought to be important in regulation of endothelial cell growth. Therefore, it is likely that the protein encoded by this gene would share some similar
20 biological functions.

When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, other immune and hematopoietic cells and tissue cell types, through the Jak-STAT signal transduction pathway. The gamma activating
25 sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and
30 differentiation of cells.

This gene is expressed in brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, nervous system disease and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 134 as residues: Thr-25 to Pro-46. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to
5 identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
10 related to SEQ ID NO:42 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general
15 formula of a-b, where a is any integer between 1 to 1150 of SEQ ID NO:42, b is an integer of 15 to 1164, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 33

20 The translation product of this gene shares sequence homology with human p150 which is thought to be important in signal transduction in neuronal cells. Therefore, it is likely that the protein encoded by this polynucleotide would share some similar biological functions with p150.

This gene is expressed primarily in whole embryo and cerebellum.

25 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological and growth defects/disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological
30 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS, expression of this gene

at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study and treatment of central nervous system, neurodevelopmental, cognitive, and memory disorders. The tissue distribution also indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Moreover, the expression within embryonic tissue and other cellular sources marked

by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:43 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1091 of SEQ ID NO:43, b is an integer of 15 to 1105, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 34

This gene is expressed primarily in PMA stimulated HL-60 cells and to a lesser extent in 6 week embryo.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting cell differentiation, particularly hematopoietic disorders and/or defects. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 136 as residues: Pro-61 to Asp-68. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study of cellular differentiation and for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia. The tissue distribution also

indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the

5 expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine

production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Moreover, the protein may

10 represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Additionally, the expression within embryonic tissue and other

15 cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the

"Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere

20 herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain

25 neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating,

30 detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue

differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:44 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1248 of SEQ ID NO:44, b is an integer of 15 to 1262, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 35

This gene is expressed primarily in colon.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders and/or defects of the digestive tract including but not limited to cancers of the gastrointestinal tract. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at

significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., gastrointestinal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders of the digestive system particularly disorders involving the colon. Further, expression of this gene product in colon tissue indicates involvement in digestion, processing, and elimination of food, as well as a potential role for this gene as a diagnostic marker or causative agent in the development of colon cancer, and cancer in general. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the colon and/or other gastrointestinal tissue including, but not limited to, stomach, small intestine, large intestine, and rectum.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:45 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 503 of SEQ ID NO:45, b is an integer of 15 to 517, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 36

This gene is expressed primarily in blood cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, immune and hematopoietic diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 138 as residues: Pro-19 to Cys-29, Thr-35 to Glu-44, Val-72 to Lys-78. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis and/or treatment of disorders of the immune and hematopoietic system. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:46 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 844 of SEQ ID NO:46, b is an

integer of 15 to 858, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 37

5 This gene is expressed in multiple tissue systems such as brain, immune cells, prostate, uterus, testes, placenta, and fetal heart as well as in cancerous tissues such as ovarian tumors. .

----- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the immune, reproductive, urogenital, and central nervous system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, 15 particularly of the central nervous system and immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, reproductive, urogenital, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative 20 to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 139 as residues: Tyr-33 to Lys-38. Polynucleotides encoding said polypeptides are also provided.

25 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders of the immune, urogenital, reproductive, and central nervous systems. The tissue distribution in central nervous system tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis 30 of diseases of the central nervous system, as well as cancers of tissues where expression of this gene has been observed, such as in ovarian tumors. The tissue

distribution in central nervous system tissues also indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in

proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The tissue distribution in uterus indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating female infertility. The protein product is likely involved in preparation of the endometrium of implantation and could be administered either topically or orally. Alternatively, this gene could be transfected in gene-replacement treatments into the cells of the endometrium and the protein products could be produced. Similarly, these treatments could be performed during artificial insemination for the purpose of increasing the likelihood of implantation and development of a healthy embryo. In both cases this gene or its gene product could be administered at later stages of pregnancy to promote healthy development of the endometrium. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The tissue distribution in testes indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product is expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed

against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:47 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 6093 of SEQ ID NO:47, b is an integer of 15 to 6107, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 38

This gene is expressed in a wide range of tissue systems such as brain, immune cells, fetal liver, kidney, testes, breast, and pancreas as well as cancerous tissue such as ovarian tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the central nervous system, immune system, urogenital, and reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, CNS, urogenital, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 140 as residues: Met-1 to Ser-7, Asp-32 to Pro-43, Ser-96 to Arg-102. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides
5 corresponding to this gene are useful for treatment and diagnosis of disorders of the immune, reproductive, urogenital and central nervous systems. The tissue distribution in central nervous system tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis
10 of diseases of the central nervous system, as well as cancers of tissues where expression of this gene has been observed, such as in ovarian tumors. The tissue distribution in central nervous system tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome,
15 schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders.
20 Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation
25 of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such
30 as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities,

such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue

differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases.

The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:48 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 689 of SEQ ID NO:48, b is an integer of 15 to 703, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 39

This gene is expressed primarily in macrophages and fetal cells and to a lesser extent in cancerous ovarian tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune diseases, disorders of developing tissues, and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in

providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetal and immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous
5 and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides
10 corresponding to this gene are useful for treatment and diagnosis of developmental abnormalities and disorders of the immune systems. The tissue distribution cancerous ovaries indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and intervention of these tumors. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker
15 and/or immunotherapy target for the above listed tissues. Expression of this gene product in macrophage cells strongly indicates a role for this protein in immune function and immune surveillance. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). This gene
20 product may have clinical utility in the treatment of immune dysfunction; in the correction of autoimmunity; in immune modulation; and in the control of inflammation.

The tissue distribution indicates polynucleotides and polypeptides
corresponding to this gene are useful for the diagnosis and treatment of a variety of
25 immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene
30 product is involved in the regulation of cytokine production, antigen presentation, or

other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the

polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of

5 degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue

10 markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The tissue distribution also indicates that polynucleotides and polypeptides corresponding to this gene are useful

15 for the treatment, diagnosis, and/or prevention of various skin disorders such as melanomas.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:49 and may have been publicly available prior to conception of

20 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 625 of SEQ ID NO:49, b is an

25 integer of 15 to 639, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 40

This gene is expressed primarily in neutrophils, bone marrow, brain, and fetal

30 cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic disorders, Limbic system disfunction/defects and disorders of the immune system and developing systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, Limbic system and developing systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 142 as residues: Ala-84 to Gln-93. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders of the immune, Limbic system, CNS and developing systems. Expression of this gene product in bone marrow, eosinophils, and neutrophils strongly indicates a role for this protein in hematopoiesis and immune surveillance. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). This gene product may have clinical utility in the treatment of immune dysfunction; in the correction of autoimmunity; in immune modulation; and in the control of inflammation. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune

Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury.

Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Additionally, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the

"Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:50 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 853 of SEQ ID NO:50, b is an

integer of 15 to 867, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 41

5 This gene is expressed primarily in ovary and to a lesser extent in fetal tissue, colon, and immune cells.

 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
10 not limited to, ovarian cancer, gastrointestinal and immune system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the female reproductive system, expression of this gene at significantly higher or lower
15 levels is routinely detected in certain tissues or cell types (e.g., reproductive, gastrointestinal, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an
20 individual not having the disorder.

 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 143 as residues: Ile-23 to Ala-29. Polynucleotides encoding said polypeptides are also provided.

 The tissue distribution indicates that polynucleotides and polypeptides
25 corresponding to this gene are useful for diagnosis and treatment of ovarian cancer and related metastases. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating female infertility. The tissue distribution in colon tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders
30 involving the gastrointestinal tract. This may include diseases associated with digestion and food absorption, as well as hematopoietic disorders involving the

Peyer's patches of the small intestine, or other hematopoietic cells and tissues within the body. Similarly, expression of this gene product in colon tissue indicates again involvement in digestion, processing, and elimination of food, as well as a potential role for this gene as a diagnostic marker or causative agent in the development of colon cancer, and cancer in general. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their

interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:51 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1555 of SEQ ID NO:51, b is an integer of 15 to 1569, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.

15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 42**

The translation product of this gene shares sequence homology with retrovirus-related reverse transcriptase pseudogene. In addition, this gene shares homology with human interferon-beta (Genseq accession number T35524; all references available through this accession are hereby incorporated herein by reference), therefore, it is likely that this gene and the protein encoded by this gene shares some similar biological functions with this protein.

This gene is expressed primarily in frontal cortex.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily

fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 5 The tissue distribution in frontal cortex and homology to retrovirus-related reverse transcriptase pseudogene and human interferon-beta indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neurodegenerative diseases of the brain, particularly of the frontal cortex. The tissue distribution indicates polynucleotides and polypeptides
- 10 corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of
- 15 Alzheimer's Disease, Parkinson's Disease, multiple sclerosis, cystic fibrosis, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder,
- 20 learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

- Potentially, this gene product is involved in synapse formation,
- 25 neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show
- 30 utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:52 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1182 of SEQ ID NO:52, b is an integer of 15 to 1196, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 43

This gene is expressed primarily in immune cells, brain, fetal tissue, and cancerous tissues (such as testes, stomach, lung, pancreas, ovaries) and to a lesser extent in other numerous tissues including, but not limited to, testes and kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and immune cells expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 145 as residues: Lys-23 to Lys-35, Met-46 to Tyr-52. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neurodegenerative disorders of the frontal cortex, as well as, cancer or a number of tissues including but not limited to testes, stomach, lung, pancreas, and ovaries. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell

lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent

of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:53 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 931 of SEQ ID NO:53, b is an integer of 15 to 945, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.

30 FEATURES OF PROTEIN ENCODED BY GENE NO: 44

This gene is expressed primarily in epithelioid sarcoma and to a lesser extent in pancreatic carcinoma, aorta endothelial cells induced with TNF-alpha, and amniotic cells induced with TNF. This gene is also expressed, to a lesser extent, in cancerous lung and ovary tissue and fetal tissue.

5 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, epithelioid sarcoma and related cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological
10 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., amniotic, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another
15 tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 146 as residues: Tyr-39 to Arg-51. Polynucleotides
20 encoding said polypeptides are also provided.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of certain cancers, including epithelioid sarcoma and pancreatic carcinoma. The tissue distribution in tumors of lung, ovary, and pancreas origins indicates that polynucleotides and
25 polypeptides corresponding to this gene are useful for the diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues. Moreover, the expression within embryonic tissue and other cellular sources marked
30 by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of

developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern
5 formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent
of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of
10 potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types
15 of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new
20 insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or
25 immunotherapy targets for the above listed tissues. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the
30 expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including

blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:54 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 474 of SEQ ID NO:54, b is an

integer of 15 to 488, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 45

5 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

PPVPPWISLPLTGSPPRPGFVPVSPFCFSPMTNGHQVLLLLLLTSAVAAGPWPQ
10 VHAGQWGWMLPPGLPSVQARSGLGGLPGGPQWVPGGARGY (SEQ ID NO:
234). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in fetal and infant tissue, particularly infant brain and fetal liver/spleen libraries, and to a lesser extent in breast, ovary tumor, pharynx carcinoma, endometrial stromal cells, thymus, islet cell tumors, and adult
15 cerebellum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer and other proliferative disorders. Similarly, polypeptides and
20 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and breast, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, developmental, hematopoietic, and cancerous and
25 wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 The tissue distribution in developing cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis

and treatment of cancer and other proliferative disorders. The expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:55 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

5 formula of a-b, where a is any integer between 1 to 2846 of SEQ ID NO:55, b is an integer of 15 to 2860, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 46

10 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

IQQWGDSVLGRRCDLLQLYLQRPRLVPVPEVLLHSEGAASSSVCKLDGLI
 15 HRFITLLADTSDSRALENRGADASMACRKLAVAHPLLLLRHLPMAALLHGR
 THLNFQEFRQQNHLSCFLHVLGLLELLQPHVFRSEHQGALWDCLLSFIRLLN
 YRKSSRHAAAFINKFVQFIHKYITYNAPAAISFLQKHADPLHDLSFDNSDLVM
 LKSLLAGLSLPSRDDRTDRGLDEEGEEESSAGSLPLVSVSLFTPLTAAEMAPY
 MKRLSRGQTVEDLLEVLSDIDEMSRRRPEILSFFSTNLQRLMSSAECCRNLA
 20 FSLALRSMQNSPSIAAAFLPTFMVCLGSQDFEVVQTALRNLPEYALLCQEHA
 AVLLHRAFLVGMYGQMDPSAQISEALRILHMEAVM (SEQ ID NO: 235).

Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in breast cancer, and to a lesser extent in a variety of other cancers, including uterine cancer, synovial sarcoma, and pharynx

25 carcinoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer; proliferative diseases and/or disorders. Similarly,

30 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For

a number of disorders of the above tissues or cells, particularly of the breast, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, breast, proliferative, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, breast milk, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 148 as residues: Glu-35 to His-41, Ser-62 to Ala-67, Pro-145 to Leu-155, Glu-157 to Ser-163, Arg-190 to Val-197, Asp-208 to Pro-215, Ser-247 to Pro-252. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in breast cancer tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of cancer. Elevated expression of this gene product in cancers, such as breast cancer, suggest that it is involved in the abnormal proliferation of cells, dedifferentiation, angiogenesis, and other processes that accompany the development of cancer. Thus, therapeutics targeted against this gene product is useful therapeutic products in and of themselves. Alternately, expression of this gene product at elevated levels in breast tissue is reflective of expression within breast lymph nodes, and may suggest a hematopoietic role for this protein. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the

polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of

5 degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue

10 markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly

15 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:56 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

20 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1545 of SEQ ID NO:56, b is an integer of 15 to 1559, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 47

The translation product of this gene shares limited sequence homology with cytochrome-c oxidase. An alternative embodiment is the polypeptide comprising the following amino acid sequence:

MLLKHLQRMVSVPPQVKASALKVVTLTANDKTSVSFSSLPGQGVIYNVIVWD

30 PFLNTSAA YIPAHTYACSFEGEGSCASLGRVSSKVFFTLFALLGFFICFFGHR

FWKTELFFIGFIIMGFFFYILITRLTPIKYDVNLILTA VTGSGVGMFLVAVVWR

FGILSICMLCVGLVLGFLISSVTFFTPLGNLKIFHDDGVFWVTFSCIAILIPVVF
 MGCLRILNILTCGVIGSYSVVLAIWSYSTLSYITLNVLKRALNKDFHRAFTN
 VPFQTNDFIILAVWGMLAVSGITLQIRRRERGRPFPPHPYKLWKQERERRVTNI
 LDPSYHIPPLRERLYGRLTQIKGLFQKEQPAGERTPLLL (SEQ ID NO: 236).

- 5 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

WARLRGPGAHARTSPQPWRGSPQAAMGFLQLLVVXVLXSEHRVAGAAE

- 10 VFGNSSEGLIEFSVGKFRYF
 ELNRPFPEEAILHDISSNVTFLIFQIHSQYQNTTVSFSPRRRSPTM (SEQ ID NO: 237). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in keratinocytes, brain, and spinal cord and to a lesser extent in hematopoietic cells and tissues.

- 15 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative disorders; hematopoietic disorders; integumentary disorders; immune dysfunction; learning disabilities. Similarly, polypeptides and
 20 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and nervous systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., integumentary, neural, developmental,
 25 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 30 The tissue distribution in brain and spinal cord cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the

diagnosis and treatment of a variety of neurological and hematopoietic disorders. For example, elevated levels of expression of this gene product in brain and spinal cord indicates that it is involved in neurodegenerative disorders. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in

5 Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms,

10 hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

15 Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Alternately, expression of this gene product in hematopoietic cells indicates that it is involved in the proliferation, differentiation, survival, and activation of all hematopoietic lineages, including stem and progenitor cells. Expression of this gene

20 product in keratinocytes indicates that it is involved in normal skin function, and could be involved in skin disorders, dermatitis, and fibrosis. The protein is useful in detecting, treating, and/or preventing congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's Disease, basal cell carcinoma, squamous cell carcinoma,

25 malignant melanoma, Paget's Disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and

30 xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox,

molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various connective tissue disorders (i.e., arthritis, trauma, tendonitis, chondromalacia and inflammation, etc.), autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, dermatomyositis, etc.), dwarfism, spinal deformation, joint abnormalities, and chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:57 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2050 of SEQ ID NO:57, b is an integer of 15 to 2064, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 48

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

30 PRVRPASPPVRSPARWGSMAGSPLLWGPRAGGVGLLVLLLLGLFRPPPALCA
RPVKEPRGLSAASPPLARLALLAASGGQCPEVRRRRGRCRPGAGAGASAGAER

QERARAEAQRLRISRRASWRSCCASGAPPATLIRLWAWTTTPTRLQRSSLALC

SAPALTLP (SEQ ID NO: 238). Polynucleotides encoding these polypeptides are also provided.

5 This gene is expressed primarily in human pituitary and to a lesser extent in pineal gland, and other areas of the brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pituitary dysfunction; abnormal growth; neurological defects; insufficient milk secretion; abnormal smooth muscle contraction. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine and nervous systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., endocrine, developmental, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, breast milk, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 150 as residues: Pro-36 to Gly-42, Pro-64 to Ala-76, Gly-83 to Ala-90, Ser-100 to Cys-108, Thr-126 to Ser-135. Polynucleotides encoding said polypeptides are also provided.

25 The tissue distribution primarily in pituitary cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of a variety of disorders. Elevated expression of this gene product in the pituitary indicates that it is possibly a hormone-like substance that either controls pituitary development itself, or various processes controlled by the pituitary. These include growth, milk secretion, smooth muscle contraction, diuresis, blood pressure, and homeostasis. Thus, this gene product may have numerous clinical

applications. Expression of this gene product in other regions of the brain also indicates that it is involved in normal neurological function, and is useful in the treatment of a variety of neurological disorders. Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", and "Binding Activity" sections below, in Example 11, 17, 18, 19, 20 and 27, and elsewhere herein. Briefly, the protein can be used for the detection, treatment, and/or prevention of Addison's Disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g. hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:58 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1036 of SEQ ID NO:58, b is an integer of 15 to 1050, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 49

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

PRVRLATPNIWDLSMLFAFISLLVMLPTWWIVSSWLVGVLVIRALRL

PZ030PCT

WRTAKLQVTLKKYSVHLEDMATNSRAFTNLVRKALRLIQETEVISRGFTLVS

AACPFNKAGQHPSQHLIGLRKAVYRTLRFANFQAARLATLYMLKNYPLNSES

DNVTNYICVVPFKELGLGLSEEQISEEEAHNFTDGFSLPALKVLFQLWVAQSS

EFFRRLALLSTANSPPGPLLTPALLPHRILSDVTQGLPHAHSACLEELKRSYE

5 FYRYFETQHQSVQCLSKTQQKSRELNNVHTAVRSLQLHLKALLNEVILEDE

LEKLVTCTKETQELVSEAYPILEQKLKLIQPHVQASNNCWEEAISQVDKLLRRN

TDKKGKPEIACENPHCTVSTFEAAYSTHCRQRSNPRGAGIRSLCR (SEQ ID

NO: 239). Polynucleotides encoding these polypeptides are also provided.

10 The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 7 - 23 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 24 to 390 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ib membrane proteins.

15 The gene encoding the disclosed cDNA is believed to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12.

This gene is expressed primarily in prostate and placenta and to a lesser extent in pancreatic tumors and hematopoietic cells.

20 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate cancer; pancreatic cancer; prostate dysfunction; hematopoietic disorders; reproductive diseases and/or disorders, and pancreatitis. Similarly,

25 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine and immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, prostate,

30 pancease, placental, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, seminal fluid, plasma, urine, synovial fluid and spinal fluid) or

another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic
5 epitopes shown in SEQ ID NO: 151 as residues: Pro-85 to Ser-94, Pro-127 to Thr-136, Glu-154 to Glu-160, Phe-240 to Ser-250, Leu-255 to Leu-265, Leu-341 to Lys-351, Thr-372 to Gly-384. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in prostate and placental cells and tissues indicates that
10 polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of a variety of reproductive disorders. Elevated expression of this gene product in the prostate indicates that it is involved in normal prostate function, and is a diagnostic marker for prostate cancer. Alternately, expression of this gene product in placenta indicates that it may play a role in normal vascular
15 function, and is involved in such processes as angiogenesis and endothelial cell chemotaxis. Thus, this gene product is useful in the treatment of myocardial infarction, cancer, ischemia, and diabetic retinopathy. Expression of this gene product in placenta may also be indicative of fetal health and development.

Similarly, expression of this gene product in hematopoietic cells indicates that
20 it is involved in the proliferation, differentiation, survival, or activation of all hematopoietic cell lineages. Finally, expression of this gene product in pancreatic cancers indicates that it may play a role in cancer in general, or in pancreatic function. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents
25 that modulate their interactions, and as nutritional supplements. It may also have a very wide range of biological activities. Representative uses are described in the "Chemotaxis" and "Binding Activity" sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Briefly, the protein may possess the following activities: cytokine, cell proliferation/differentiation modulating activity or
30 induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases

and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating
5 infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's Disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as,
10 antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:59 and may have been publicly available prior to conception of
15 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2519 of SEQ ID NO:59, b is an
20 integer of 15 to 2533, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 50

When tested against Jurkat and K562 cell lines, supernatants removed from
25 cells containing this gene activated the GAS (gamma activating sequence) and ISRE (interferon-sensitive responsive element) promoter elements, respectively. Thus, it is likely that this gene activates myeloid, leukemia, and to a lesser extent, other immune or hematopoietic cells and tissue cell-types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes
30 which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells.

Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. ISRE is also a promoter element found upstream in many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

AAPHPLLRPLCLWCPLWPAWPLRGRPSAWKRWPLPVGPAKLGCSMTTR
OPTAVSWPCWLMSSSLSTACLAWTLTGSLAREATRRARSLSPWNCSARQV
PPSPPHSGLGRRGWAHCHLT CLLVTQLFRVGRIHPILSLPLVT (SEQ ID NO:
240). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in brain and placenta.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, vascular diseases; aberrant angiogenesis; neurological disorders; learning disorders; placental insufficiency; and fetal distress. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular and neurological systems (CNS/PNS), expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, reproductive, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 152 as residues: Met-1 to Thr-7, Glu-36 to Ser-43,
5 Pro-46 to Gly-63. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain and placental cells and tissues, combined with the detected GAS and ISRE biological activities, indicates that the protein products of this gene are useful for the diagnosis and/or treatment of a variety of neural, reproductive, and vascular diseases and/or disorders. neurodegenerative disease
10 states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis,
15 encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and
20 perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Expression of this gene product in placenta indicates that it may play a role
25 in blood vessel development or function, as the placenta is a highly vascularized organ. Thus, this gene product is involved in such processes as angiogenesis, endothelial cell chemotaxis, and vascular cord formation. Thus, it is useful in the treatment of such conditions as myocardial infarction; ischemia; and cancer. Alternately, expression of this gene product in the brain indicates that it may play a
30 role in the survival, proliferation, or function of neurons, and thus is useful in the diagnosis and treatment of such neurological disorders as ALS, schizophrenia, and

Alzheimer's Disease. It may likewise be involved in learning disorders as well.

Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

- 5 Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:60 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 885 of SEQ ID NO:60, b is an integer of 15 to 899, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 51

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

LQLASQSAGIKGMSHCARPTFLTLLLASCFWAAIPNRNVILSVSFRPLHMQ
FTLSILVFILRILILRSFL (SEQ ID NO: 241). Polynucleotides encoding these

25 polypeptides are also provided.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 40 - 56 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 57 to 60 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

This gene is expressed primarily in spleen derived from patients with chronic lymphocytic leukemia.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, chronic lymphocytic leukemia; hematopoietic disorders; impaired immune function; cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in spleen cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of a variety of hematopoietic disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Elevated expression of this protein in the spleens of patients with CLL indicates that it is a useful marker for this Disease. Alternately, it is associated with the development and/or progression of the disease, and is a useful target for therapeutic intervention. Additionally, this gene

product may play more general roles in hematopoiesis, and may serve to control cellular decisions regarding proliferation, survival, activation, and/or differentiation of all hematopoietic cell lineages. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate
5 ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
10 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:61 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
15 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1065 of SEQ ID NO:61, b is an integer of 15 to 1079, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.

20 **FEATURES OF PROTEIN ENCODED BY GENE NO: 52**

The translation product of this gene shares sequence homology with a putative tyrosine protein kinase from the Chilo iridescent virus. See, for example, Genbank accession no. gi|2738451 (AF003534). Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities
25 with tyrosine kinase and signaling proteins. Such activities are known in the art, some of which are described elsewhere herein.

This gene is expressed in a variety of tissues, including microvascular endothelial cells, dendritic cells, and fetal tissues. as well as several tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as
30 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, vascular, immune, and developmental diseases and/or disorders, particularly cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above

5 tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., vascular, immune, developmental, proliferative, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having

10 such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 154 as residues: Ala-21 to Lys-31, Arg-41 to Cys-56, Thr-92 to Cys-102, Arg-132 to Val-137, Lys-152 to Ile-159, Pro-199 to Ser-205, Arg-

15 210 to Asp-219, Ser-225 to Lys-230, Tyr-236 to Ala-241, Lys-243 to Leu-249, Thr-375 to Asp-381. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution and homology to a tyrosine kinase indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of cancer. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27,

20 and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes

25 suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such

30 as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities,

such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the protein is useful in the detection, treatment, and/or prevention of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs or regulates the survival of neighboring neurons. Likewise, it is involved in controlling the digestive process, and such actions as peristalsis. Similarly, it is involved in controlling the vasculature in areas where smooth muscle surrounds the endothelium of blood vessels. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:62 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1914 of SEQ ID NO:62, b is an

integer of 15 to 1928, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 53

5 The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 2 - 18 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ib membrane proteins.

 This gene is expressed primarily in neutrophils.

10 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic diseases and/or disorders, particularly cancer and immune suppression. Similarly, polypeptides and antibodies directed to
15 these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids
20 (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

 Preferred polypeptides of the present invention comprise immunogenic
25 epitopes shown in SEQ ID NO: 155 as residues: Gly-63 to Ser-72. Polynucleotides encoding said polypeptides are also provided.

 The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful as a marker for neutrophil monitoring in cancer and/or immune suppressed patients and/or during chemotherapy
30 or radiation therapy. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and

elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:63 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 767 of SEQ ID NO:63, b is an integer of 15 to 781, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.

5

FEATURES OF PROTEIN ENCODED BY GENE NO: 54

This gene is expressed primarily in IL-1 and LPS induced neutrophils, and to a lesser extent, in fetal brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, hematopoietic, and neural diseases and/or disorders, particularly cancer and immune suppression. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 156 as residues: Ile-28 to Trp-37, Ser-68 to Lys-81. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful as a marker in neutrophils to monitor patients who are immune suppressed or cancer patients during chemotherapy or radiation therapy. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in

regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:64 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1180 of SEQ ID NO:64, b is an integer of 15 to 1194, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 55

This gene is expressed primarily in prostate.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, urogenital diseases and/or disorders, particularly prostate cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the urogenital system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., urogenital, prostate, renal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 157 as residues: Arg-30 to Gln-36. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in prostate cancer cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for study, treatment and diagnosis of prostate cancer and other urogenital disorders. Moreover, the expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis,

treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:65 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1663 of SEQ ID NO:65, b is an integer of 15 to 1677, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.

5

FEATURES OF PROTEIN ENCODED BY GENE NO: 56

A preferred polypeptide of the invention comprises the following amino acid sequence:

MVLVLRHPLCARERAFREPGRGLLTRTGQHDGAPAVTAVPGPLGAVAAAEG
10 RRSAGWAGGSSPPRKVLWGDMRGRRAGVDVLGPALSSEAAGAEARGWGM
PGMGVGVGASETRGALFLGREGVHGPCPMDGLGPWPWGPW (SEQ ID NO:
242). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in rejected kidney.

Therefore, polynucleotides and polypeptides of the invention are useful as
15 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders affecting the kidney. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of
20 disorders of the above tissues or cells, particularly of the urinary tract, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., urogenital, renal, kidney, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative
25 to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 158 as residues: Ala-30 to Gly-36, Asp-45 to Trp-50, Lys-65 to Cys-71, Pro-80 to Cys-87. Polynucleotides encoding said polypeptides are
30 also provided.

The tissue distribution in kidney indicates the protein product of this gene could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. The protein is useful for modulating the immune response to aberrant proteins, as may exist in proliferating cells and tissues. Such modulation of the immune response would also show utility in inhibiting the rejection of transplanted tissues, particularly of the renal system. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:66 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1223 of SEQ ID NO:66, b is an integer of 15 to 1237, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 57

The translation product of this gene shares sequence homology with both human and mouse Fibulin-2 which is an extracellular matrix protein found in heart tissue (See Genbank Accession Nos. emb|CAA57876.1 and emb|CAA53040.1, respectively; all references available through these accessions are hereby incorporated

herein by reference; for example, J. Cell Biol. 123 (5), 1269-1277 (1993)). Preferred polypeptides encoded by this gene comprise the following amino acid sequence:

MGPAVKMWTNAWKGLDDCHYNQLCENTPGGHRCSGPRGYRMQGPSLPCL
 DVNECLQLPKACAYQCHNLQGSYRCLCPPGQTLLRDGKACTSLERNQNVT
 5 TVSHRGPLLPWLRPWASIPGTSYHAWVSLRPGPMALSSVGRAWCPPGFIRQN
 GVCTDLDECRVRNLCQHACRNTEGSYQCLCPAGYRLLPSGKNCQDINECEEE
 SIECGPGQMCFNTRGSYQCVDTPCPATYRQGSPGTCFRRCSQDCGTGGPSTL
 QYRLLPLPLGVRAHHDVARLTAFASEVGPANRTELSMLEPDPRSPFALRPLRA
 GLGAVYTRRALTRAGLYRLTVRAAAPRHQSVFVLLIAVSPYPY (SEQ ID NO:
 10 243). Polynucleotides encoding these polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following amino acid sequence:

MRVLVVTIPIYWALARESGEALNGHSLTGGKFRQSHTWSLLQGAHDDPV
 ARGDPDGLLLLDVVVNGVVPRAWLTQIFKCRCLKKHVYVQTRAWPAVRG
 15 LHTALLPGRPPLVPTLQPQHPVQRGPGPPAPAGAAPAGLSYQLGL (SEQ ID
 NO: 244). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the

20 following amino acid sequence:

HASGAFLVVRGEPQGSWSMTGVINGRKFGVATLNTSVMQEAHSGVSSIHSS
 IRHVPANVGPLMRVLVVTIPIYWALARESGEALNGHSLTGGKFRQESHVEF
 ATGELLTMTQWPGVWIPMASCSSTWWSMALSPDSLADADLQVQDFEEHYV
 QTGPGQLFVGSTQRFFQGGLPSFLRCNHSIQYNAARGPQPQLVQHLRASAIS
 25 AFDPEAEALRFQLATALQAEENEVGCPEGFELDSQGAFCVDVDECAWDAHL
 CREGQRCVNLLGSYRCLPDCGPGFRVADGAGCEDVDECLEGLDDCHYNQLC
 ENTPGGHRCSGPRGYRMQGPSLPCLDVNECLQLPKACAYQCHNLQGSYRCL
 CPPGQTLLRDGKACTSLERNQNVTTVSHRGPLLPWLRPWASIPGTSYHAWV
 SLRPGPMALSSVGRAWCPPGFIRQNGVCTDLDECRVRNLCQHACRNTEGSY
 30 QCLCPAGYRLLPSGKNCQDINECEEEESIECGPGQMCFNTRGSYQCVDTPCPAT
 YRQGSPGTCFRRCSQDCGTGGPSTLQYRLLPLPLGVRAHHDVARLTAFASEV

GVPANRTELSMLEPDPRSPFALRPLRAGLGAVYTRRALTRAGLYRLTVRAAA
PRHQSVMFVLLIAVSPYPY (SEQ ID NO: 245). Polynucleotides encoding these
polypeptides are also provided.

When tested against U937 and Jurkat cell lines, supernatants removed from
5 cells containing this gene repeatedly activated the GAS (gamma activating sequence)
promoter element. Thus, it is likely that this gene activates myeloid, T-cells, and to a
lesser extent, other immune and hematopoietic cells and tissue cell types, through the
JAK-STAT signal transduction pathway. GAS is a promoter element found upstream
of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway
10 is a large, signal transduction pathway involved in the differentiation and proliferation
of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of
the GAS element, can be used to indicate proteins involved in the proliferation and
differentiation of cells.

This gene is expressed primarily in kidney.

15 Therefore, polynucleotides and polypeptides of the invention are useful as
reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
not limited to, diseases and/or disorders affecting the kidney and renal system.
Similarly, polypeptides and antibodies directed to these polypeptides are useful in
20 providing immunological probes for differential identification of the tissue(s) or cell
type(s). For a number of disorders of the above tissues or cells, particularly of the
urinary tract, expression of this gene at significantly higher or lower levels is
routinely detected in certain tissues or cell types (e.g., renal, urogenital, kidney, and
cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,
25 synovial fluid and spinal fluid) or another tissue or cell sample taken from an
individual having such a disorder, relative to the standard gene expression level, i.e.,
the expression level in healthy tissue or bodily fluid from an individual not having the
disorder.

Preferred polypeptides of the present invention comprise immunogenic
30 epitopes shown in SEQ ID NO: 159 as residues: Lys-32 to Ser-37, His-89 to Gly-94,
Asn-124 to Gln-130, Ala-163 to Val-168, Cys-196 to Arg-201, Gln-244 to Gln-264,

His-288 to Tyr-294, Leu-314 to Gln-319, Ala-392 to Ser-399, Pro-412 to Asp-419, Ala-452 to Pro-460, Arg-466 to Thr-473. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in rejected kidney, the homology to the conserved

5 Fibulin-2 protein, in addition to the detected GAS biological activity, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting kidneys, particularly proliferative disorders. Representative uses are described here and elsewhere herein. The protein

10 product of this gene could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Furthermore, the protein may also be used

15 to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:67 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

25 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1920 of SEQ ID NO:67, b is an integer of 15 to 1934, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 58

Preferred polypeptides of the invention comprise the following amino acid

sequence:

MGEKFLLLAMKENHPECFCCKILKILHCMDPGEWLPQTEHCVHLPKEFLIWT
MDIASNERSEIQSVALRLASKVISHMQTCVENRELIAAELKQWVQLVILSCE
5 DHLPTESRLAVVEVLTSTTPLFLTNPPILELQDTLALWKCVLTLQSEEQAV
RDAATETVTTAMSQENTCQSTEF AFCQVDASIALALALAVLCDLLQQWDQL
APGLPILLGWLLGESDDL VACVESMHQVEEDYLFEKAEVNFWAETLIFVKYL
CKHLFCLLSKSGWRPPSPEMLCHLQRMVSEQCHLLSQFFRELPPAAEFVKTV
EFTRLRIQEERTLACLRLAFLEGKEGEDTLVLSVWDSYAESRQLTLPRTEAA
10 C (SEQ ID NO: 246). Polynucleotides encoding such polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following
amino acid sequence: MGEPNRHPSM

FLLLLVLERLYASPM DGTSSALSMGPFVPFIMRCGHSPVYHSREMAARALVP
FVMIDHIPNTIRTLLSTL
15 PSCTDQCFRAKPHSWG HFSRFFHLLQAYSDSKTRNEFRLPARAD (SEQ ID NO:
247). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of
the open reading frame upstream of the predicted signal peptide are contemplated by
the present invention. Specifically, polypeptides of the invention comprise the

20 following amino acid sequence:

MTGREFFSRFPELYPFLLKQLETVANTVDS DMGEPNRHPSMFLLLLVLERLY
ASPM DGTSSALSMGPFVPFIMRCGHSPVYHSREMAARALVPFVMIDHIPNTIR
TLLSTLP SCTDQCFRQNHIGTLLQVFHLLQAYSDSKHGTNSDFQHELT DITV
CTKAKLWLAKRQNPCLVTRAVYIDILFLTCLNRS AKDNQPVLES LGFWEE
25 VRGIISGSELITGFPWAFKVPGLPQYLQSLTRLAIAAVWAAA AKSGERETNVPI
SFSQLLES AFPEVRSLTLEALLEKFLAAASGLGEKGVPLL CNMGEKFLLLAM
KENHPECFCCKILKILHCMDPGEWLPQTEHCVHLPKEFLIWTMDIASNERSEIQ
SVALRLASKVISHMQTCVENRELIAAELKQWVQLVILSCEDHLPTESRLAVV
EVL TSTTPLFLTNPPILELQDTLALWKCVLTLQSEEQAVRDAATETVTTAM
30 SQENTCQSTEF AFCQVDASIALALALAVLCDLLQQWDQLAPGLPILLGWLLG
ESDDL VACVESMHQVEEDYLFEKAEVNFWAETLIFVKYLCKHLFCLLSKSG

WRPPSPEMLCHLQRMVSEQCHLLSQFFRELPPAAEFVKTVEFTRLRIQEERTL
 ACLRLLAFLEGKEGEDTLVLSVWDSYAESRQLTLPRTEAAC (SEQ ID NO:

248). Polynucleotides encoding these polypeptides are also provided.

The polypeptide of this gene has been determined to have two transmembrane
 5 domains at about amino acid position 144 - 160, and 462 - 478 of the amino acid
 sequence referenced in Table 1 for this gene. Based upon these characteristics, it is
 believed that the protein product of this gene shares structural features to type IIIa
 membrane proteins. Included in this invention as a preferred domain is the formate
 and nitrite transporters domain, which was identified using the ProSite analysis tool
 10 (Swiss Institute of Bioinformatics). A number of bacterial and archaeobacterial
 proteins involved in transporting formate or nitrite have been shown [1] to be related:
 - *focA* and *focB*, from *Escherichia coli*, transporters involved in the bidirectional
 transport of formate. - *fdhC*, from *Methanobacterium formicicum* and
thermoformicicum, a probable formate transporter. - *nirC*, from *Escherichia coli* and
 15 *Salmonella typhimurium*, a probable nitrite transporter. - *Bacillus subtilis*
 hypothetical protein *yrhG*. - *Bacillus subtilis* hypothetical protein *ywcJ* (ipa-48R).
 These transporters are proteins of about 280 residues and seem to contain six
 transmembrane regions. As signature patterns, we selected two conserved regions.
 The first one is located in what seems to be a cytoplasmic loop between the second
 20 and third transmembrane domains; the second is part of the fourth transmembrane
 region. The 70 Kd yeast hypothetical protein YHL008c is highly similar, in its N-
 terminal section, to the prokaryotic members of this family. The consensus pattern is
 as follows: [LIVMA]-[LIVMY]-x-G-[GSTA]-[DES]-L-[FI]-[TN]-[GS].

Preferred polypeptides of the invention comprise the following amino acid
 25 sequence: IISGSELITG (SEQ ID NO: 249). Polynucleotides encoding these
 polypeptides are also provided. Further preferred are polypeptides comprising the
 formate and nitrite transporter domain of the sequence referenced in Table for this
 gene, and at least 5, 10, 15, 20, 25, 30, 50, or 75 additional contiguous amino acid
 residues of this referenced sequence. The additional contiguous amino acid residues is
 30 N-terminal or C-terminal to the formate and nitrite transporter domain. Alternatively,
 the additional contiguous amino acid residues is both N-terminal and C-terminal to

the formate and nitrite transporter domain, wherein the total N- and C-terminal contiguous amino acid residues equal the specified number. The above preferred polypeptide domain is characteristic of a signature specific to formate and nitrite transporter proteins. Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with formate and nitrite transporter proteins. Such activities are known in the art, some of which are described elsewhere herein. It is believed that this gene maps to chromosome 2. Accordingly, polynucleotides derived from this gene are useful in linkage analysis as markers for chromosome 2.

10 This gene is expressed primarily in cells of the immune system, primarily T-cells and to a lesser extent in spleen, liver, thymus, tonsils, and testis.

 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic diseases and/or disorders, particularly disorders affecting hematopoiesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of hematopoietic cells, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 160 as residues: Gly-2 to Pro-8, Ser-82 to His-92, Tyr-107 to Asp-117, Arg-162 to Pro-169, Ser-224 to Thr-229, Leu-310 to His-315, Ser-333 to Glu-338, Glu-381 to Ser-388, Gln-428 to Ala-433, Met-446 to Thr-455, Ser-548 to Ser-554, Gly-613 to Asp-618, Ser-627 to Gln-633. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in immune cells and tissues indicates that

polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting hematopoiesis, including cancers. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:68 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
 5 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3286 of SEQ ID NO:68, b is an integer of 15 to 3300, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.

10 FEATURES OF PROTEIN ENCODED BY GENE NO: 59

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

15 VDGIDKLDIEFLQQFLETHSRGPR LHSPGHASQEATPGANMSSGTELLWPGAA
 LLVLLGVAASLCVRCSRPGAKRSEKIYQQRSLREDQQSFTGSRTYSLVGQAW
 PGPLADMAPTRKDKLLQFYPSLEDPASSRYQNFSKGSRHGSEEAYIDPIAMEY
 YNWGRFSKPPEDDDANSYENVLICKQKTTETGAQQEGIGGLCRGDLSSLAL
 KTGPTSGLCPSASPEEDEGI (SEQ ID NO: 250). Polynucleotides encoding these
 20 polypeptides are also provided.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 10 - 26 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ib membrane proteins.

25 The gene encoding the disclosed cDNA is believed to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

This gene is expressed primarily in bone marrow, CD34 positive cells, and immune cells, including, neutrophils, T-cells, B-cells, macrophages, monocytes, and
 30 dendritic cells and to a lesser extent in brain and tonsils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting the immune and hematopoietic systems, particularly hematopoiesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the the immune system and hematopoeitic system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 161 as residues: Ser-29 to Thr-57, Pro-74 to Lys-79, Pro-85 to Glu-107, Tyr-118 to Tyr-136, Gln-144 to Gln-152, Ala-182 to Glu-188. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in immune and hematopoietic cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for

immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, and as nutritional supplements. It may also have a very wide range of biological activities.

Representative uses are described in the "Chemotaxis" and "Binding Activity" sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Briefly, the protein may possess the following activities: cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors);

hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's Disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the
5 corresponding nucleic acid in gene therapy procedures.

Based upon the the proteins immune cell specific message distribution, it may be involved
in many aspects of the immune response, especially its initial stages, inflammation, allograft rejection, infectious disease response etc. The expression of this clone is
10 frequently found in the hematopoietic cell cDNA libraries. Thus, this factor could be involved in the control of hematopoietic cell proliferation, differentiation, and function. Based on this one can postulate its use in the management of anemias, leukemias, neutropenia, thrombocytopenia, autoimmune
diseases, blood tissue engraftment, and poikilothromerythromatosis. Furthermore, the
15 protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:69 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
25 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1783 of SEQ ID NO:69, b is an integer of 15 to 1797, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 60

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

5 VLVREASALVLSNRLSSGLLHDLLLQPAIHSRLFRRSRGLSEGE GSSVSLQRS
RVLSAMKHVLNLYLLGVVLTLLSIFVRVMESLEGLLESPPGTSWTTTSQLAN
TEPTKGLPDHPSRSM (SEQ ID NO: 251). Polynucleotides encoding these

polypeptides are also provided.

This gene is expressed primarily in immune cells including activated T cells,
10 macrophages, jurkat cells, bone marrow cells, and osteoblasts and to a lesser extent in kidney cortex, brain, placenta and lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
15 not limited to, immune and hematopoietic diseases and/or disorders, particularly inflammation and diseases related to inflammatory activity. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression
20 of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in
25 healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 162 as residues: Pro-34 to Met-63. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in immune cells and tissues indicates that
30 polynucleotides and polypeptides corresponding to this gene are useful for treating or diagnosing disease related to the normal or abnormal activation of T cells.

Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein.

Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell

- 5 lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

- Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for
- 10 immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity
- 15 disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful
- 20 in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as,
- 25 antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:70 and may have been publicly available prior to conception of
- 30 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1359 of SEQ ID NO:70, b is an integer of 15 to 1373, where both a and b correspond to the positions of nucleotide
5 residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 61

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by
10 the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

YTFHTQIFLDFPMIFLTVLPLAFLFLHSGFYHYISFSLFSLSLALFFFLDVATFR
RPGQLFCERSVLFDMMFHFGFVSLFLHEWIQAKHFWAGLF
IVLPSDVFFSVHHLEAPDGSFPNIAKLSLIILLR (SEQ ID NO: 252).

15 Polynucleotides encoding these polypeptides are also provided.

The polypeptide of this gene has been determined to have two transmembrane domains at about amino acid position 2 - 18 and 22 - 38 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type IIIa membrane
20 proteins.

This gene is expressed in many tissues including brain, liver, prostate, testes, cartilage, gall bladder. Expression is also seen in a number of tumors including colon carcinoma, pancreas tumor, osteoclastoma, ovarian cancer, B cell lymphoma and acute lymphocytic leukemias.

25 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, tumors of various organs including the pancreas, colon, and bone. Similarly, polypeptides and antibodies directed to these polypeptides are useful in
30 providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the

major organs, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, hepatic, metabolic, reproductive, testicular, skeletal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or
5 another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors and proliferative tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating or
10 diagnosing tumors of several major organs including the pancreas and large intestine. This protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below
15 and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain
20 neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating,
25 detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in
30 proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the

protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:71 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1565 of SEQ ID NO:71, b is an integer of 15 to 1579, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 62

This gene is expressed primarily in dendritic cells and fetal liver/spleen and to a lesser extent in many tissues including tonsils, fetal lung, stromal cell lines, bone marrow cell lines, placenta and tumors including hepatocellular carcinoma, pancreas tumor and osteosarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders of the immune and hematopoietic system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,

synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5 The tissue distribution in dendritic cells and fetal liver/spleen indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing and treating disorders of the immune system particularly related to the control and generation of precursor cells. polynucleotides and polypeptides
10 corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow
15 transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

 The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of
20 stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies
25 directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:72 and may have been publicly available prior to conception of
30 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1014 of SEQ ID NO:72, b is an integer of 15 to 1028, where both a and b correspond to the positions of nucleotide
5 residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 63

This gene is expressed primarily in adrenal gland tumor and endothelial cells.

Therefore, polynucleotides and polypeptides of the invention are useful as
10 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endocrine and vascular diseases and/or disorders, particularly diseases associated with the vascular endothelium. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for
15 differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., endocrine, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or
20 cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in endothelial cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing and treating
25 disorders that involve the vascular system including diseases such as atherosclerosis, neoangiogenesis associated with tumor growth and conditions associated with inflammation. Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke,
30 embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Alternatively, the protein is useful in the treatment, detection, and/or

prevention of metabolic disorders, particularly lethargy and depression. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:73 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3660 of SEQ ID NO:73, b is an integer of 15 to 3674, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 64

The translation product of this gene is related to bovine PAM precursor. See Genbank record gi|163482 incorporated herein by reference. Moreover, see following patent publications are also incorporated herein by reference: J04311386 and WO8902460. Many bioactive peptides terminate with an amino acid alpha-amide at their COOH terminus. The enzyme responsible for this essential posttranslational modification is known as peptidyl-glycine alpha-amidating monooxygenase or PAM. An NH₂-terminal signal sequence and short propeptide precede the NH₂ terminus of purified PAM. The sequences of several PAM cyanogen bromide peptides were localized in the NH₂-terminal half of the predicted protein. The forms of PAM purified from bovine neurointermediate pituitary is generated by endoproteolytic cleavage at a subset of the 10 pairs of basic amino acids in the precursor. High levels of PAM mRNA have been found in bovine pituitary and cerebral cortex. In

corticotropin tumor cells, levels of PAM mRNA and pro-ACTH/endorphin mRNA are known to be regulated in parallel by glucocorticoids and CRF.

This gene is expressed primarily in endometrial tumors, dendritic cells, a multiple sclerosis library, kidney, hematopoietic cells, melanocytes, osteoblasts, the spleen, colon, ovary, stromal cells, fetal and adult brain, heart, and in tissues undergoing wound repair.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endometriosis, endometrial cancer, multiple sclerosis, hematopoietic diseases, bone disease, and wound healing. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly the hematopoietic system and female reproduction, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., reproductive, immune, hematopoietic integumentary, skeletal, gastrointestinal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in dendritic and hematopoietic cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful as a therapeutic or diagnostic agent in diseases of hematopoietic origin as well as the female reproductive tract due to the gene's primary pattern of expression. polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses

include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency
5 etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The protein may also have a very wide range of biological activities. Representative uses are described in the "Chemotaxis" and "Binding Activity" sections below, in Examples 11, 12, 13, 14, 15,
10 16, 18, 19, and 20, and elsewhere herein. Briefly, the protein may possess the following activities: cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to
15 chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock,
20 Crohn's Disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:74 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is
30 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 2783 of SEQ ID NO:74, b is an integer of 15 to 2797, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 65

The translation product of this gene shares sequence similarity with several G-protein coupled receptors (See Genbank Accession No. gb|AAC77910.1|

(AF061443); all references available through this accession are hereby incorporated herein by reference; for example, Mol. Endocrinol. 12, 1830-1845 (1998)). G-protein

10 coupled receptors are well known in the art and affect a variety of functions. In particular, the translation product of this gene shares similarity with Follicular Stimulating Hormone Receptor.

Preferred polypeptides encoded by this gene comprise the following amino acid sequence:

15 GTRFPTGETPSLGFTVTLVLLNSLAFLLMAYIYTKLYCNLEKEDLSENSQSSMI
KHVAWLIFTNCIFFCPVAFFSFAPLITAISISPEIMKSVTLIFFP (SEQ ID NO:
253). Polynucleotides encoding such polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following amino acid sequence: MIKHVAWLIFTNCIFFCP

20 VAFFSFAPLITAISISPEIMKSVTLIFFPCLLA (SEQ ID NO: 254). Polynucleotides encoding these polypeptides are also provided.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the

25 following amino acid sequence:

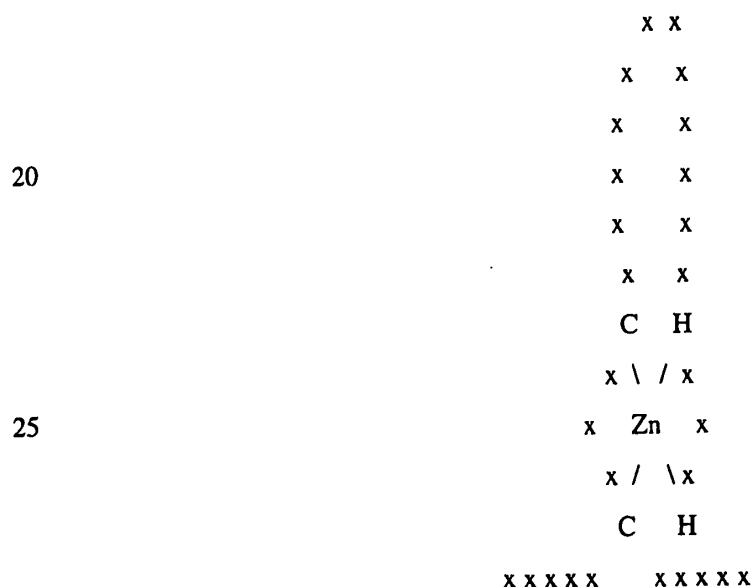
GTRFPTGETPSLGFTVTLVLLNSLAFLLMAYIYTKLYCNLEKEDLSENSQSSMI
KHVAWLIFTNCIFFCPVAFFSFAPLITAISISPEIMKSVTLIFFPLPACLNPNVLYVF
FNPKFEDWKLLKRRVTKSGSVSVSISSQGGCLEQDFYYDCGMYSHLQGN
LTVCDCCESFLLTKPVSKHLIKSHSCPALAVASCQRPEGYWSDCGTQSAHS
30 DYADEEDSFVSDSSDQVQACGRACFYQSRGFPLVRYAYNLPRVKD (SEQ ID
NO: 255). Polynucleotides encoding these polypeptides are also provided.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 43 - 59 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 60 to 207 of this protein has also been determined. Based upon these characteristics, it is

5 believed that the protein product of this gene shares structural features to type Ia membrane proteins. Included in this invention as preferred domains are Zinc finger, C2H2 type domains, which were identified using the ProSite analysis tool (Swiss Institute of Bioinformatics). 'Zinc finger' domains [1-5] are nucleic acid-binding

10 protein structures first identified in the *Xenopus* transcription factor TFIIIA. These domains have since been found in numerous nucleic acid-binding proteins. A zinc finger domain is composed of 25 to 30 amino-acid residues. There are two cysteine or histidine residues at both extremities of the domain, which are involved in the tetrahedral coordination of a zinc atom. It has been proposed that such a domain

15 domain is shown below:



30 Many classes of zinc fingers are characterized according to the number and positions of the histidine and cysteine residues involved in the zinc atom

coordination. In the first class to be characterized, called C2H2, the first pair of zinc coordinating residues are cysteines, while the second pair are histidines. A number of experimental reports have demonstrated the zinc- dependent DNA or RNA binding property of some members of this class. Some of the proteins known to include

5 C2H2-type zinc fingers are listed below. We have indicated, between brackets, the number of zinc finger regions found in each of these proteins; a '+' symbol indicates that only partial sequence data is available and that additional finger domains is present. In addition to the conserved zinc ligand-residues it has been shown that a number of other positions are also important for the structural integrity of the C2H2

10 zinc fingers. The best conserved position is found four residues after the second cysteine; it is generally an aromatic or aliphatic residue. The consensus pattern is as follows: C-x(2,4)-C-x(3)-[LIVMFYWC]-x(8)-H-x(3,5)-H.

Preferred polypeptides of the invention comprise the following amino acid sequence: CDCCESFLLTKPVSCKHLIKSH (SEQ ID NO: 256). Polynucleotides

15 encoding these polypeptides are also provided. Further preferred are polypeptides comprising the Zinc finger, C2H2 type domain of the sequence referenced in Table for this gene, and at least 5, 10, 15, 20, 25, 30, 50, or 75 additional contiguous amino acid residues of this referenced sequence. The additional contiguous amino acid residues is N-terminal or C- terminal to the Zinc finger, C2H2 type domain.

20 Alternatively, the additional contiguous amino acid residues is both N-terminal and C-terminal to the Zinc finger, C2H2 type domain, wherein the total N- and C-terminal contiguous amino acid residues equal the specified number. The above preferred polypeptide domain is characteristic of a signature specific to zinc finger proteins. Based on the sequence similarity, the translation product of this gene is expected to

25 share at least some biological activities with G-coupled proteins, their receptors, and zinc finger proteins. Such activities are known in the art, some of which are described elsewhere herein.

This gene is expressed primarily in adult and fetal liver, human placenta, colon carcinoma cell lines and fibroblasts and to a lesser extent in the fetal and adult

30 brain, the developing nervous system, lung, pancreas, salivary gland, breast tissue, and dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the liver, developmental abnormalities, neurologic diseases,

5 lung cancer, pancreatic cancer, and colon cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurological and hepatic origin, as well as the proliferation and/or differentiation of numerous types of tissues.
10 expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., hepatic, immune, hematopoietic, neural, gastrointestinal, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative
15 to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 167 as residues: Pro-62 to Asp-67, Arg-74 to Gly-80, Gln-146 to Glu-168. Polynucleotides encoding said polypeptides are also provided.

20 The tissue distribution in fetal liver indicates that polynucleotides and polypeptides corresponding to this gene are useful for a diagnostic marker or therapeutic in a wide variety of disease states. polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or
25 leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of
30 neoplasia.

The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the

5 differentiation and/or proliferation of various cell types. Alternatively, the protein expression in placental and brain tissue indicates the protein is useful in the detection, treatment, and/or prevention of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism. For example, this gene product may represent a soluble

10 factor produced by smooth muscle that regulates the innervation of organs or regulates the survival of neighboring neurons. Likewise, it is involved in controlling the digestive process, and such actions as peristalsis. Similarly, it is involved in controlling the vasculature in areas where smooth muscle surrounds the endothelium of blood vessels. The protein is useful in the treatment, detection, and/or prevention of

15 bacterial, fungal, protozoan and viral infections, particularly infections caused by HIV-1 or HIV-2; pain; cancers; anorexia; bulimia; asthma; Parkinson's Disease; acute heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ulcers; allergies; benign prostatic hypertrophy; and psychotic and neurological disorders, including anxiety, schizophrenia, manic

20 depression, delirium, severe mental retardation and dyskinesias, such as Huntington's Disease or Gilles de la Tourette's syndrome. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed

25 against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:75 and may have been publicly available prior to conception of

30 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2689 of SEQ ID NO:75, b is an integer of 15 to 2703, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 66

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

ALENSGSPGLQDSARAHFNXSLRSFSFLRNQMYIFELSLYLEGTSFVVLLFLL
ISVSLDSPPTTKGWDSVLHIWVPLIVQ (SEQ ID NO: 257). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in placenta and in hematopoietic cells, especially those of T-cell and monocyte origin and to a lesser extent in the brain, endothelial cells, and the lungs.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic, vascular, and developmental diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., vascular, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 168 as residues: Ser-30 to Trp-37. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in hematopoietic cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for therapeutic and/or diagnostic intervention in hematopoietic and developmental disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the protein is useful in the detection, treatment, and/or prevention of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs or regulates the survival of neighboring neurons. Likewise, it is involved in controlling the digestive process, and such actions as peristalsis. Similarly, it is involved in controlling the vasculature in areas where smooth muscle surrounds the endothelium of blood vessels. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:76 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 728 of SEQ ID NO:76, b is an integer of 15 to 742, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 67

10 This gene is expressed primarily in the prostate and to a lesser extent in in human B-cell lymphomas.

 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate cancer and diseases of hematopoietic origin, particularly of B-cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the prostate and immune systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., prostate, reproductive, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, seminal fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 169 as residues: Asp-33 to Lys-42. Polynucleotides encoding said polypeptides are also provided.

 The tissue distribution in prostate tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful as a therapeutic or diagnostic marker for prostate cancer and disorders involving hematopoietic cells, especially

30

those of B-cell origin. Moreover, the expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. The protein is useful in modulating the immune response to aberrant proteins and polypeptides, as may exist in rapidly proliferating cells and tissues. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:77 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1811 of SEQ ID NO:77, b is an integer of 15 to 1825, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 68

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:
GHESICGSCRSWIYFSIRCRRRMRPWWSLLLEACATCAQTGPTRSTSCTQEVS
HSSSTAYPAPMRRRCCL PSPRSCT (SEQ ID NO: 258). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

~~This gene is expressed primarily in the brain and the developing embryo and to a lesser extent in the heart, colon, adipose tissue, kidney, mammary tissue, activated T-cells and dendritic cells.~~

Therefore, polynucleotides and polypeptides of the invention are useful as
5 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological diseases, developmental conditions, colon cancer, and hematopoietic diseases, especially of T-cell origin. Similarly, polypeptides and
10 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., neural, developmental, cardiovascular, adipose, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g.,
15 lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic
20 epitopes shown in SEQ ID NO: 170 as residues: Thr-18 to Cys-26, Glu-29 to Thr-36, Ser-50 to Thr-55. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in brain, combined with the detected GAS biological activity, indicates that polynucleotides and polypeptides corresponding to this gene are useful for therapeutic and/or diagnostic agents in neurological diseases,
25 developmental abnormalities, colon cancer, and hematopoietic diseases, especially those of T-cell origin. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease,
30 Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal

cord-injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated
5 expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity,
10 to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
15 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:78 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or
20 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1660 of SEQ ID NO:78, b is an integer of 15 to 1674, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 69

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 2 - 18 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein
30 product of this gene shares structural features to type II membrane proteins.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise the following amino acid sequence:

5 K R A G V E V G G L V M A L A G S V F V L G G V L V L C V E R N G E G E M G W P Q H L P K S Q P L S
P P V A V R R C S F E R S W I D L L V E T S S S M V T C R Q Q V G T P N G M E G R G G G P K T T F P I R L
Q L S G A C A V R P E I Q W E V (SEQ ID NO: 259). Polynucleotides encoding these polypeptides are also provided.

This gene is expressed primarily in activated monocytes, dendritic cells, and
10 in the tonsils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic diseases and/or disorders, particularly
15 leukemia, lymphomas, tumors of hematopoietic origin. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic system, expression of this gene at significantly higher or lower levels is routinely detected in
20 certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 171 as residues: Gln-30 to Leu-38, Asn-75 to Thr-86. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution in activated monocytes, dendritic cells, and tonsils indicates that polynucleotides and polypeptides corresponding to this gene are useful
30 as a therapeutic and/or diagnostic agent for leukemias, lymphomas, and other diseases associated with cells of hematopoietic origin. Representative uses are described in the

"Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:79 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is

cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2177 of SEQ ID NO:79, b is an integer of 15 to 2191, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 70

When-tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, other immune cells and tissue cell types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

The gene encoding the disclosed cDNA is believed to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12.

This gene is expressed primarily in the placenta, brain, and liver and to a lesser extent in most other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic, neurological, vascular, and developmental diseases and/or disorders, particularly cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and nervous systems, expression of this gene at significantly higher or lower levels is routinely detected in certain tissues or

cell-types (e.g., hematopoietic, neurological, vascular, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, bile, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful therapeutic and/or diagnostic agent in a multitude of disease states, particularly those involving the immune and neurologic systems. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:80 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1321 of SEQ ID NO:80, b is an integer of 15 to 1335, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 71

The translation product of this gene shares sequence homology with the murine Fig1 (interleukin-four induced gene 1) which shares homology to the monoamine oxidases, particularly in domains responsible for FAD binding. Preferred polypeptides encoded by this gene comprise the following amino acid sequence:

QDWKAERSQDPFEKCMQDPDYEQLLKVTILEADNRIGGRIFTYRDQXTGWIG
 ELGAMRMPSSHRILHKLCQGLGLNLTKFTQYDKNTWTEVHEXKLRNYVVEK
 VPEKLG YALRPQEKGHSPEDIYQMALNQALKDLKALGCRKAMKKFERHTLL
 EYLLGEGNLSRPAVQLLGDVMSSEGGFFYLSFAEALRAXSCLSDRLQYSRIVG
 GWDLLPRALLSSLSGLVLLNAPVVAMTQGPHDVHVQIETSPARNLKV LKAD
 VVLLTASGPAVKRITFS (SEQ ID NO: 260), and/or

LPRHMQEALRRLHYVPATKVFLSFRPFWREEHIEGGHSNTDRPSRMIFYPPP
 REGALLASYTWSDAAAAFAGLSREEALRLALDDVAALHGPVVRQLWDGT
 GVVKRWAEDQHSQGGFVVQXPALWQTEKDDWTVPYGRIYFAGEHTAYPHG
 WVETAVKSALRAAIKINSRKGPASDTASPEGHASDMEGQGHVHGVASSPSH
 DLAKEEGS (SEQ ID NO: 261). Polynucleotides encoding such polypeptides are also provided.

A preferred polypeptide fragment of the invention comprises the following

amino acid sequence:

MAPLALHLLVLPILLSLVASQDWKAERSQDPFEKCMQDPDYEQLLKVTIL
 EADNRIGGRIFTYRDQXTGWIGELGAMRMPSSHRILHKLCQGLGLNLTKFTQ
 5 YDKNTWTEVHEXKLRNYVVEKVPEKLGALRPQEKGHSPEDIYQMALNQA
 LKDLKALGCRKAMKKFERHTLLEYLLGEGNLSRPAVQLLGDVMSSEDGFFYL
 SFAEALRAXSCLSDRLQYSRIVGGWDLPRALLSSLSGLVLLNAPVVAMTQG
 PHDVH
 VQIETSPARNLKVLKADVLLTASGPAVKRITFSPRCPATCRRRCGGCTTCR

10 PPRCS (SEQ ID NO: 262). Based on the sequence similarity, the translation product of this gene is expected to share at least some biological activities with monoamine oxidases, disintegrins, metalloproteinases, and apoptosis modulating proteins. Such activities are known in the art, some of which are described elsewhere herein.

Polynucleotides encoding these polypeptides are also provided.

15 The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 235 - 251 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 252 to 319 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia
 20 membrane proteins.

This gene is expressed primarily in hematopoietic cells, particularly in dendritic cells, and activated monocytes and to a lesser extent in T-cells, endothelial cells, and cells associated with ulcerative colitis.

Therefore, polynucleotides and polypeptides of the invention are useful as
 25 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, leukemias, lymphomas, and diseases associated with antigen presenting cells, in addition to apoptosis dependant events. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological
 30 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression

of this gene at significantly higher or lower levels is routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 173 as residues: Gln-22 to Gln-44, Ala-90 to Gly-95, Lys-137 to Trp-146, Arg-171 to Asp-181, Glu-370 to Ser-380, Asp-447 to Gly-452, Gln-463 to Trp-469, Asn-504 to Ala-510, Asp-512 to His-519, Ala-541 to Val-550, Asn-558 to His-566. Polynucleotides encoding said polypeptides are also provided.

The tissue distribution immune and hematopoietic cells and tissues, combined with the homology to the murine Fig 1 gene indicates that polynucleotides and polypeptides corresponding to this gene are useful as a therapeutic and/or diagnostic agent for hematopoietic diseases, especially those associated with antigen presenting cells. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's

Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:81 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1853 of SEQ ID NO:81, b is an integer of 15 to 1867, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HISCN02	209878 05/18/98	pSport1	11	1113	1	1113	232	232	103	1	26	27	106
2	HHGDM70	209878 05/18/98	Lambda ZAP II	12	983	102	983	69	69	104	1	57	58	86
3	HHPGO40	209878 05/18/98	Uni-ZAP XR	13	973	1	973	68	68	105	1	37	38	302
3	HHPGO40	209878 05/18/98	Uni-ZAP XR	82	984	1	984	74	74	174	1	37	38	224
4	HAMGG68	209878 05/18/98	pCMVSPORT 3.0	14	1458	1	1458	312	312	106	1	20	21	55
5	HAPOM49	209878 05/18/98	Uni-ZAP XR	15	2005	1	2005	251	251	107	1	22	23	189
5	HAPOM49	209878 05/18/98	Uni-ZAP XR	83	2664	1	2664	448	448	175	1	1	2	123
6	HBGBA69	209878 05/18/98	Uni-ZAP XR	16	943	1	933	62	62	108	1	38	39	60
7	HBJFJ26	209878 05/18/98	Uni-ZAP XR	17	1503	588	1480	290	290	109	1	26	27	128

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	5' NT of Clone Seq.	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
7	HBJFJ26	209878 05/18/98	Uni-ZAP XR	84	1328	413	1305	591	176	1	20	21	59
8	HCEDH38	209878 05/18/98	Uni-ZAP XR	18	1512	1	1438	222	110	1	26	27	68
9	HDPOJ08	209878 05/18/98	pCMVSPORT 3.0	19	1655	1	1655	159	111	1	18	19	122
10	HDPRX82	209878 05/18/98	pCMVSPORT 3.0	20	2525	1	2525	128	112	1	32	33	82
11	HELKGK31	209878 05/18/98	Uni-ZAP XR	21	1396	25	1334	209	113	1	29	30	344
11	HCNUA40	97898 02/26/97 209044 05/15/97	pBluescript	85	1342	949	1237	960	177	1	33	34	105
12	HFPCX64	209878 05/18/98	Uni-ZAP XR	22	1069	1	1069	181	114	1	28	29	181
12	HFPCX64	209878 05/18/98	Uni-ZAP XR	86	1154	84	1154	257	178	1	28	29	87
12	HCEBW71	209225 08/28/97	Uni-ZAP XR	87	1197	141	1197	257	179	1	28	29	87

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
13	HFXDO60	209878 05/18/98	Lambda ZAP II	23	1658	1	1658	131	131	115	1	46	47	115
14	HHEPG41	209878 05/18/98	pCMVSPORT 3.0	24	1077	385	1043	514	514	116	1	35	36	70
14	HAUAI83	209626 02/12/98	Uni-ZAP XR	88	910	1	886	253	253	180	1	37	38	49
14	HJPAZ83	209626 02/12/98	Uni-ZAP XR	89	1076	398	1076		575	181	1	11	12	23
15	HKGAH42	209878 05/18/98	pSport1	25	1205	1	1205	143	143	117	1	21	22	63
16	HMIAP86	209878 05/18/98	Uni-ZAP XR	26	1674	13	1674	182	182	118	1	19	20	334
17	HMUAP70	209878 05/18/98	pCMVSPORT 3.0	27	1965	531	1914	183	183	119	1	16	17	221
17	HMUAP70	209878 05/18/98	pCMVSPORT 3.0	90	1842	407	1783	413	413	182	1	25	26	103
17	HAGFY16	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	91	1963	209	1922	251	251	183	1	28	29	198

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
17	HBMCF37	209683 03/20/98	pBluescript	92	1487	79	1487	170	170	184	1	44	45	70
17	HFLQB16	209641 02/25/98	Uni-ZAP XR	93	1653	394	1637	413	413	185	1	25	26	82
17	HAGFY16	97923 03/07/97	Uni-ZAP XR	94	1830	87	1786	128	128	186	1	26	27	45
18	HRACJ35	209878 05/18/98	pCMVSPORT 3.0	28	1863	8	1863	99	99	120	1	24	25	472
18	HAWAZ34	209141 07/09/97	pBluescript SK-	95	1134	472	1132	687	687	187	1			33
19	HTWDE26	209878 05/18/98	pSport1	29	1626	1	1626	68	68	121	1	30	31	167
19	HMHBN40	97901 02/26/97 209047 05/15/97	Uni-ZAP XR	96	1772	69	1772	129	129	188	1	30	31	231
20	HUSIB13	209878 05/18/98	pSport1	30	605	1	605	172	172	122	1	32	33	46
21	HBAFA02	209877 05/18/98	pSport1	31	931	359	931	46	46	123	1	21	22	108

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
22	H2CBT75	209877 05/18/98	pBluescript SK-	32	1407	1	1407	32	32	124	1	23	24	60
23	HAGDQ42	209877 05/18/98	Uni-ZAP XR	33	1526	1	1526	126	126	125	1	18	19	248
24	HBMCI42	209877 05/18/98	pBluescript	34	1737	41	1580	244	244	126	1	44	45	248
25	HDPBQ71	209877 05/18/98	pCMVSPORT 3.0	35	2242	6	2242	24	24	127	1	33	34	612
26	HCEJG71	209877 05/18/98	Uni-ZAP XR	36	2235	2	2235	28	28	128	1	25	26	447
27	HELHL48	209877 05/18/98	Uni-ZAP XR	37	2971	560	2557	629	629	129	1	16	17	291
27	HSKCT36	209580 01/14/98	Uni-ZAP XR	98	1955	1	1955	31	31	190	1	18	19	184
28	HISAQ04	209877 05/18/98	pSport1	38	1163	1	1163	61	61	130	1	21	22	78
29	HJACB89	209877 05/18/98	pBluescript SK-	39	1932	28	1930	95	95	131	1	23	24	333
30	HTECC05	209877 05/18/98	Uni-ZAP XR	40	881	1	881	27	27	132	1	15	16	164

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
31	HBJLF01	209877 05/18/98	Uni-ZAP XR	41	1932	201	1931	217	217	133	1	46	47	244
32	HBXGP60	209877 05/18/98	ZAP Express	42	1164	1	1164	143	143	134	1	22	23	55
33	HCE5B20	209877 05/18/98	Uni-ZAP XR	43	1105	1	1105	237	237	135	1	25	26	54
34	HCMSQ56	209877 05/18/98	Uni-ZAP XR	44	1262	1	1262	148	148	136	1	19	20	88
35	HCNAH57	209877 05/18/98	Lambda ZAP II	45	517	1	517	35	35	137	1	33	34	61
36	HCUEP91	209877 05/18/98	ZAP Express	46	858	2	858	266	266	138	1	20	21	105
37	HDP CJ91	209877 05/18/98	pCMVSPORT 3.0	47	6107	1	6107	131	131	139	1	28	29	51
38	HDP GK25	209877 05/18/98	pCMVSPORT 3.0	48	703	1	703	345	345	140	1	33	34	119
39	HE2DY70	209877 05/18/98	Uni-ZAP XR	49	639	1	639	137	137	141	1	45	46	58
40	HE2NV57	209877 05/18/98	Uni-ZAP XR	50	867	1	867	99	99	142	1	36	37	99

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
41	HETBR16	209877 05/18/98	Uni-ZAP XR	51	1569	1	1569	161	161	143	1	21	22	64
42	HFXDG13	209877 05/18/98	Lambda ZAP II	52	1196	1	1196	43	43	144	1	37	38	66
43	HFXKY27	209877 05/18/98	Lambda ZAP II	53	945	1	945	44	44	145	1	19	20	58
44	HHPEC09	209877 05/18/98	Uni-ZAP XR	54	488	1	488	71	71	146	1	19	20	55
45	HISAD54	209877 05/18/98	pSport1	55	2860	1	2860	172	172	147	1	19	20	65
46	HJBCY35	209877 05/18/98	pBluescript SK-	56	1559	93	1272	232	232	148	1	23	24	327
47	HKAEA19	209877 05/18/98	pCMVSPORT 2.0	57	2064	1	1909	83	83	149	1	21	22	89
48	HKGDL36	209877 05/18/98	pSport1	58	1050	1	1050	55	55	150	1	33	34	148
49	HLDBS43	209877 05/18/98	pCMVSPORT 3.0	59	2533	1	2533	73	73	151	1	26	27	390
50	HLWAD92	209877 05/18/98	pCMVSPORT 3.0	60	899	1	899	197	197	152	1	34	35	98

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
51	HLYBI15	209877 05/18/98	pSport1	61	1079	1	1079	92	92	153	1	22	23	60
52	HMEJE05	209889 05/22/98	Lambda ZAP II	62	1928	1	1928	25	25	154	1	30	31	392
53	HNGIX55	209889 05/22/98	Uni-ZAP XR	63	781	1	781	121	121	155	1	19	20	74
54	HNHEX30	209889 05/22/98	Uni-ZAP XR	64	1194	1	1194	138	138	156	1	15	16	81
55	HPJBI33	209889 05/22/98	Uni-ZAP XR	65	1677	1	1677	236	236	157	1	31	32	53
56	HRABA80	209889 05/22/98	pCMVSPORT 3.0	66	1237	1	1237	130	130	158	1	28	29	102
57	HRACD80	209889 05/22/98	pCMVSPORT 3.0	67	1934	1	1934	191	191	159	1	16	17	575
57	HRACD80	209889 05/22/98	pCMVSPORT 3.0	99	1958	1	1958	191	191	191	1	16	17	146
58	HSLCX03	209889 05/22/98	Uni-ZAP XR	68	3300	984	2729	677	677	160	1	22	23	643
58	HSLCX03	209889 05/22/98	Uni-ZAP XR	100	2444	1	2444	392	392	192	1	22	23	124

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
59	HT5GJ57	209889 05/22/98	Uni-ZAP XR	69	1797	92	1797	122	122	161	1	25	26	190
60	HTACS42	209889 05/22/98	Uni-ZAP XR	70	1373	1	1373	213	213	162	1	29	30	63
61	HTEKE40	209889 05/22/98	Uni-ZAP XR	71	1579	1	1579	173	173	163	1	47	48	117
62	HTOBX69	209889 05/22/98	Uni-ZAP XR	72	1028	1	1028	28	28	164	1	20	21	42
63	HUVEO77	209889 05/22/98	Uni-ZAP XR	73	3674	1	3674	55	55	165	1	27	28	47
64	H2CBG48	209889 05/22/98	pBluescript SK-	74	2797	1	2797	125	125	166	1	25	26	45
65	H2CBU83	209889 05/22/98	pBluescript SK-	75	2703	1	2703	157	157	167	1	30	31	207
65	H2CBU83	209889 05/22/98	pBluescript SK-	101	2709	1	2709	157	157	193	1	30	31	51
66	HAPNY94	209889 05/22/98	Uni-ZAP XR	76	742	1	742	94	94	168	1	29	30	50
67	HBJHZ58	209889 05/22/98	Uni-ZAP XR	77	1825	1	1825	102	102	169	1	29	30	42

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
68	HCE2B33	209889 05/22/98	Uni-ZAP XR	78	1674	1	1668	67	67	170	1	18	19	55
69	HDPBQ02	209889 05/22/98	pCMVSPORT 3.0	79	2191	291	2191	460	460	171	1	24	25	108
70	HF1Y170	209889 05/22/98	pSPORT1	80	1335	1	1335	43	43	172	1	15	16	50
71	HDPOZ56	209889 05/22/98	pCMVSPORT 3.0	81	1867	415	1867	103	103	173	1	21	22	566
71	HDPOZ56	209889 05/22/98	pCMVSPORT 3.0	102	1722	1	1722	59	59	194	1	21	22	319

Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further

below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to the secreted proteins encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed

sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are species homologs. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for the desired homologue.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural or recombinant sources using antibodies of the invention raised against the secreted protein in methods which are well known in the art.

Signal Sequences

Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, Virus Res. 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, Nucleic Acids Res. 14:4683-4690 (1986) uses the

information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, supra.) However, the two
5 methods do not always produce the same predicted cleavage point(s) for a given protein.

In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10:1-6 (1997)), which predicts the cellular location of a
10 protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1.

As one of ordinary skill would appreciate, however, cleavage sites sometimes
15 vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., + or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely
20 uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the
25 naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

30 **Polynucleotide and Polypeptide Variants**

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

5 By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the
10 polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire
15 sequence shown in Table 1, the ORF (open reading frame), or any fragment specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known
20 computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences
25 are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty
30 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95%

"identical" to a query amino-acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid.

These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequences shown in Table 1 or to the amino acid sequence encoded by deposited DNA clone can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the the

query sequence, the percent-identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter

the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred.

Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced

5 for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an

10 organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level.

Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA
15 technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., *J. Biol. Chem.* 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after
20 deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., *J. Biotechnology* 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological
25 activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (*J. Biol. Chem.* 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every
30 possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See,

Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as to have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used.

(Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of the present invention having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course, in order of ever-increasing preference, it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of the present invention, which contains at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of the present invention or fragments thereof (e.g., the mature form and/or other fragments described herein), is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

15

Polynucleotide and Polypeptide Fragments

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clone or shown in SEQ ID NO:X. The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in the deposited clone or the nucleotide sequence shown in SEQ ID NO:X. These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

25

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-

30

1300, 1301-1350, ~~1351-1400~~, ~~1401-1450~~, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, ~~1901-1950~~, ~~1951-2000~~, or 2001 to the end of SEQ ID NO:X or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or
5 smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

In the present invention, a "polypeptide fragment" refers to a short amino acid
10 sequence contained in SEQ ID NO:Y or encoded by the cDNA contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-
15 40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

20 Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the
25 mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotide fragments encoding these polypeptide fragments are also preferred.

30 Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and

- alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions.
- 5 Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotide fragments encoding these domains are also contemplated.

- Other preferred fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.
- 10

Epitopes & Antibodies

- 15 In the present invention, "epitopes" refer to polypeptide fragments having antigenic or immunogenic activity in an animal, especially in a human. A preferred embodiment of the present invention relates to a polypeptide fragment comprising an epitope, as well as the polynucleotide encoding this fragment. A region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." In contrast, an "immunogenic epitope" is defined as a part of a protein that elicits an antibody response. (See, for instance, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983).)
- 20

- Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)
- 25

- In the present invention, antigenic epitopes preferably contain a sequence of at least seven, more preferably at least nine, and most preferably between about 15 to about 30 amino acids. Antigenic epitopes are useful to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe, J. G. et al., Science 219:660-666 (1983).)
- 30

Similarly, immunogenic epitopes can be used to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow, M. et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle, F. J. et al., J. Gen. Virol. 66:2347-2354 (1985).) A preferred immunogenic epitope includes the secreted protein. The immunogenic epitopes may be presented together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough (at least about 25 amino acids), without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting.)

As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')₂ fragments) which are capable of specifically binding to protein. Fab and F(ab')₂ fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl et al., J. Nucl. Med. 24:316-325 (1983).) Thus, these fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library. Moreover, antibodies of the present invention include chimeric, single chain, and humanized antibodies.

20

Fusion Proteins

Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous

30

functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Moreover, polypeptides of the present invention, including fragments, and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., Nature 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995).)

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See,

D. Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); K. Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide.

- 5 In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein.
- 10 Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., *Cell* 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

15

Vectors, Host Cells, and Protein Production

- The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral
- 20 vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

- The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate,
- 25 such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

- The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli* lac, trp, phoA and tac
- 30 promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The

expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or
5 UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples
10 of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-
15 9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1
20 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods
25 are described in many standard laboratory manuals, such as Davis et al., *Basic Methods In Molecular Biology* (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from
30 recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography,

phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

5 Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant,
10 insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine
15 encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

20 In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide
25 sequences) that is operably associated with the polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24,
30 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al.,

Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

5

Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

10 The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

15 Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids
20 containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides
25 can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome specific-cDNA libraries.

Precise chromosomal location of the polynucleotides can also be achieved
30 using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however,

polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques." Pergamon Press, New York (1988).

5 For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides correspond to the noncoding regions of the cDNAs because the coding sequences are more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

10 Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and
15 one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined.
20 First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide
25 and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using
30 polynucleotides of the present invention. Any of these alterations (altered expression,

chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Both methods
5 rely on binding of the polynucleotide to DNA or RNA. For these techniques, preferred polynucleotides are usually 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J.
10 Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can
15 be used to design antisense or triple helix polynucleotides in an effort to treat disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate
20 manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel.
25 In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA
30 markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using
5 this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification
10 techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co.
15 (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

20 There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by
25 organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences
30 in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA

antibodies using DNA-immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

5 Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

 A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M.,
10 et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell. Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such
15 as iodine (^{125}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{112}In), and technetium ($^{99\text{m}}\text{Tc}$), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

 In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo
20 imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for
25 the relevant hybridoma.

 A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I , ^{112}In , $^{99\text{m}}\text{Tc}$), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or
30 intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety

needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein.

- 5 In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which
10 involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder.

- 15 Moreover, polypeptides of the present invention can be used to treat disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B), to inhibit the activity of a polypeptide (e.g., an oncogene), to
20 activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth).

- Similarly, antibodies directed to a polypeptide of the present invention can
25 also be used to treat disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

- At the very least, the polypeptides of the present invention can be used as
30 molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also

be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

5

Biological Activities

The polynucleotides and polypeptides of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides could be used to treat the associated disease.

10

Immune Activity

A polypeptide or polynucleotide of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, a polynucleotide or polypeptide of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

15

20

25

30

A polynucleotide or polypeptide of the present invention may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. A polypeptide or polynucleotide of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency,

~~Digeorge Syndrome, HIV-infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.~~

5 Moreover, a polypeptide or polynucleotide of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotide or polypeptide of the present invention could be used to treat blood
10 disorders (e.g. afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, a polynucleotide or polypeptide of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

15 A polynucleotide or polypeptide of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of a polypeptide or polynucleotide of the
20 present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

 Examples of autoimmune disorders that can be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic
25 anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary
30 Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by a polypeptide or polynucleotide of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

A polynucleotide or polypeptide of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, a polypeptide or polynucleotide of the present invention may also be used to modulate inflammation. For example, the polypeptide or polynucleotide may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

Hyperproliferative Disorders

A polypeptide or polynucleotide can be used to treat or detect hyperproliferative disorders, including neoplasms. A polypeptide or polynucleotide of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, a polypeptide or polynucleotide of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune
5 response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but are not limited to
10 neoplasms located in the: abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by
15 a polynucleotide or polypeptide of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenström's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia,
20 located in an organ system listed above.

Infectious Disease

A polypeptide or polynucleotide of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response,
25 particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, the polypeptide or polynucleotide of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

30 Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the

present invention. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Pasteurellaceae Infections (e.g., Actinobacillus, Haemophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis,

opportunistic-infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, 5 Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

10 Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and 15 Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these 20 symptoms or diseases.

Preferably, treatment using a polypeptide or polynucleotide of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the 25 patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

30 A polynucleotide or polypeptide of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See,

Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, 5 reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration 10 occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, a polynucleotide or polypeptide of the present invention may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. A polynucleotide or polypeptide of the present invention could also be used 15 prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using a 20 polynucleotide or polypeptide of the present invention to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral 25 neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotide or polypeptide of the present invention.

30

Chemotaxis

A polynucleotide or polypeptide of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

A polynucleotide or polypeptide of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that a polynucleotide or polypeptide of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, a polynucleotide or polypeptide of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable

of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

All of these above assays can be used as diagnostic or prognostic markers.

The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptide from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a

- candidate-binding compound with a polypeptide of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

Other Activities

- A polypeptide or polynucleotide of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

- A polypeptide or polynucleotide of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide or polynucleotide of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

- A polypeptide or polynucleotide of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, cardiac rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

- A polypeptide or polynucleotide of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

Other Preferred Embodiments

- Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95%

identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under
5 stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which
10 comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide
15 sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of
20 at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

25 A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule
30 comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

~~A further preferred embodiment is a method for detecting in a biological~~
sample a nucleic acid molecule comprising a nucleotide sequence which is at least
95% identical to a sequence of at least 50 contiguous nucleotides in a sequence
selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X
5 wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by
a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained
in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table
1; which method comprises a step of comparing a nucleotide sequence of at least one
nucleic acid molecule in said sample with a sequence selected from said group and
10 determining whether the sequence of said nucleic acid molecule in said sample is at
least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences
comprises determining the extent of nucleic acid hybridization between nucleic acid
molecules in said sample and a nucleic acid molecule comprising said sequence
15 selected from said group. Similarly, also preferred is the above method wherein said
step of comparing sequences is performed by comparing the nucleotide sequence
determined from a nucleic acid molecule in said sample with said sequence selected
from said group. The nucleic acid molecules can comprise DNA molecules or RNA
molecules.

20 A further preferred embodiment is a method for identifying the species, tissue
or cell type of a biological sample which method comprises a step of detecting nucleic
acid molecules in said sample, if any, comprising a nucleotide sequence that is at least
95% identical to a sequence of at least 50 contiguous nucleotides in a sequence
selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X
25 wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by
a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained
in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table
1.

The method for identifying the species, tissue or cell type of a biological
30 sample can comprise a step of detecting nucleic acid molecules comprising a
nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least

one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

- Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the
- 5 Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

- Further preferred is an isolated polypeptide comprising an amino acid
- 10 sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

- 15 Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

- 20 Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

- 25 Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

- 30 Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in

the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence
5 at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a
10 polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained
15 in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group
20 consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least
25 one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence
30 selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide

comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino

acid-sequence-of-SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

- 5 In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

25 Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

30 Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is

expressed-and-recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of

5 SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1

10 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an

15 isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

20

Examples

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector.

25 Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being

30 isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

	<u>Vector-Used-to-Construct Library</u>	<u>Corresponding Deposited</u>
	<u>Plasmid</u>	
	Lambda Zap	pBluescript (pBS)
	Uni-Zap XR	pBluescript (pBS)
5	Zap Express	pBK
	lafmid BA	plafmid BA
	pSport1	pSport1
	pCMVSPORT 2.0	pCMVSPORT 2.0
	pCMVSPORT 3.0	pCMVSPORT 3.0
10	pCR [®] 2.1	pCR [®] 2.1
	<p>Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.</p>	
25	<p>Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain</p>	
30		

XL-1 Blue Vector pCR[®]2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ³²P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for

bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the
5 SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the
3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired
cDNA using the deposited cDNA plasmid as a template. The polymerase chain
reaction is carried out under routine conditions, for instance, in 25 μ l of reaction
mixture with 0.5 μ g of the above cDNA template. A convenient reaction mixture is
10 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 μ M each of dATP, dCTP, dGTP, dTTP, 25
pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR
(denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1
min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The
amplified product is analyzed by agarose gel electrophoresis and the DNA band with
15 expected molecular weight is excised and purified. The PCR product is verified to be
the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding
portions of a gene which may not be present in the deposited clone. These methods
include but are not limited to, filter probing, clone enrichment using specific probes,
20 and protocols similar or identical to 5' and 3' "RACE" protocols which are well
known in the art. For instance, a method similar to 5' RACE is available for
generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et
al., *Nucleic Acids Res.* 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a
25 population of RNA presumably containing full-length gene RNA transcripts. A
primer set containing a primer specific to the ligated RNA oligonucleotide and a
primer specific to a known sequence of the gene of interest is used to PCR amplify
the 5' portion of the desired full-length gene. This amplified product may then be
sequenced and used to generate the full length gene.

30 This above method starts with total RNA isolated from the desired source,
although poly-A+ RNA can be used. The RNA preparation can then be treated with

phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction
5 leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific
10 to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

15 A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

Example 3: Tissue Distribution of Polypeptide

20 Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P³² using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After
25 labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H)
30 or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to

manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70°C overnight, and the films developed according to standard procedures.

5 **Example 4: Chromosomal Mapping of the Polynucleotides**

 An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is
10 repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in
15 the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

 A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA
20 sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc.,
25 Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

 The pQE-9 vector is digested with BamHI and XbaI and the amplified
30 fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain

M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and
5 confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.⁶⁰⁰) of between 0.4 and 0.6. IPTG
10 (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic
15 agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The
20 QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

25 The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4,
30 containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250

mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains:

- 1) a neomycinphosphotransferase gene as a selection marker,
- 2) an *E. coli* origin of replication,
- 3) a T5 phage promoter sequence,
- 4) two lac operator sequences,
- 5) a Shine-Delgarno sequence, and
- 6) the lactose operon repressor gene (*lacIq*).

The origin of replication (*oriC*) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with *NdeI* and *XbaI*, *BamHI*, *XhoI*, or *Asp718*, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for *NdeI* (5' primer) and *XbaI*, *BamHI*, *XhoI*, or *Asp718* (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM

Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate
5 is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the
10 pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA
15 by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The
20 filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

25 Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40
30 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium

acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 μ g of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

10

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in

30

Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in
5 Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment
10 then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a
15 commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified
20 by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five μ g of a plasmid containing the polynucleotide is co-transfected with 1.0 μ g of a commercially available linearized baculovirus DNA ("BaculoGold™
25 baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One μ g of BaculoGold™ virus DNA and 5 μ g of the plasmid are mixed in a sterile well of a microtiter plate containing 50 μ l of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 μ l Lipofectin plus 90 μ l Grace's medium are
30 added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded

in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

- 5 After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell
- 10 culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded
- 15 in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

- To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of
- 20 infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 µCi of ³⁵S-methionine and 5 µCi ³⁵S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation.
- 25 The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

30 **Example 8: Expression of a Polypeptide in Mammalian Cells**

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a

chromosome. Chinese-hamster-ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession
5 No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the
10 polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

15 A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

20 The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and
25 purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for
30 transfection. Five μ g of the expression plasmid pC6 is cotransfected with 0.5 μ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo

contains a dominant selectable-marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μ M, 2 μ M, 5 μ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

15 Example 9: Protein Fusions

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the half-life time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

30 Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These

primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be
5 destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

10 If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

15 Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACCTCACACATGCCACCGTGC
CCAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTCCCCCAAAA
CCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGT
GGTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGG
20 ACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTA
CAACAGCACGTACCGTGTGGTCAGCGTCCTACCGTCCTGCACCAGGACT
GGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCA
ACCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAG
25 GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGT
GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCT
CCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTG
GACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG
30 GTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

Example 10: Production of an Antibody from a Polypeptide

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) For example, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is

possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody

- 5 whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

- It will be appreciated that Fab and F(ab')₂ and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic
- 15 chemistry.

- For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)
- 20

25

Example 11: Production Of Secreted Protein For High-Throughput Screening Assays

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described in

- 30 Examples 13-20.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at 2×10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37°C for 6 hours.

While cells are incubating, prepare appropriate media, either 1% BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl₂ (anhyd); 0.00130 mg/L CuSO₄·5H₂O; 0.050 mg/L of Fe(NO₃)₃·9H₂O; 0.417 mg/L of FeSO₄·7H₂O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl₂; 48.84 mg/L of MgSO₄; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO₃; 62.50 mg/L of NaH₂PO₄·H₂O; 71.02 mg/L of Na₂HPO₄; .4320 mg/L of ZnSO₄·7H₂O; .002 mg/L of Arachidonic Acid; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H₂O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H₂O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H₂O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H₂O; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B₁₂; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37°C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

- 5 On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

15 Example 12: Construction of GAS Reporter Construct

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

20 GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class 1, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

30 The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2,

Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

	<u>Ligand</u>	<u>tyk2</u>	<u>JAKs</u> <u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>	<u>STATS</u>	<u>GAS(elements) or ISRE</u>
	<u>IFN family</u>						
5	IFN-a/B	+	+	-	-	1,2,3	ISRE
	IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
	Il-10	+	?	?	-	1,3	
	<u>gp130 family</u>						
10	IL-6 (Pleiotrophic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
	Il-11(Pleiotrophic)	- ?	+	?	?	1,3	
	OnM(Pleiotrophic)	?	+	+	?	1,3	
	LIF(Pleiotrophic)	?	+	+	?	1,3	
	CNTF(Pleiotrophic)	-/+	+	+	?	1,3	
15	G-CSF(Pleiotrophic)	?	+	?	?	1,3	
	IL-12(Pleiotrophic)	+	-	+	+	1,3	
	<u>g-C family</u>						
	IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
20	IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
	IL-7 (lymphocytes)	-	+	-	+	5	GAS
	IL-9 (lymphocytes)	-	+	-	+	5	GAS
	IL-13 (lymphocyte)	-	+	?	?	6	GAS
	IL-15	?	+	?	+	5	GAS
25	<u>gp140 family</u>						
	IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
	IL-5 (myeloid)	-	-	+	-	5	GAS
	GM-CSF (myeloid)	-	-	+	-	5	GAS
30	<u>Growth hormone family</u>						
	GH	?	-	+	-	5	
	PRL	?	+/-	+	-	1,3,5	
	EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
35	<u>Receptor Tyrosine Kinases</u>						
	EGF	?	+	+	-	1,3	GAS (IRF1)
	PDGF	?	+	+	-	1,3	
	CSF-1	?	+	+	-	1,3	GAS (not IRF1)
40							

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI-site. The sequence of the 5' primer is:

10 5': GCGCCTCGAGATTTCCTCCCGAAATCTAGATTTCCTCCCGAAATGATTTCCTCCCGAAATGATTTCCTCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5': GCGGCAAGCTTTTGGCAAAGCCTAGGC:3' (SEQ ID NO:4)

15 PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

20 5': CTCGAGATTTCCTCCCGAAATCTAGATTTCCTCCCGAAATGATTTCCTCCCGAAATGATTTCCTCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCT
25 AGGCTTTTGGCAAAGCTT:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol

30

acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

25

Example 13: High-Throughput Screening Assay for T-cell Activity.

The following protocol is used to assess T-cell activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells

30

(ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-
5 SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected.
Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is
10 demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1% Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life
15 Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1×10^7 cells in OPTI-MEM to T25
20 flask and incubate at 37°C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing a polypeptide as produced by the protocol described in
25 Example 11.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100
30 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100,000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred
5 directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed
10 in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20°C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4°C and serve as a source
15 of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

The above protocol may be used in the generation of both transient, as well as,
20 stable transfected cells, which would be apparent to those of skill in the art.

Example 14: High-Throughput Screening Assay Identifying Myeloid Activity

The following protocol is used to assess myeloid activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate
25 myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

30 To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell

Growth & Differentiation, 5:259-265)-is used. First, harvest 2×10^7 U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

- 5 Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$, 1 mM MgCl_2 , and 675 uM CaCl_2 . Incubate at 37°C for 45 min.

- 10 Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37°C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

- 15 These cells are tested by harvesting 1×10^8 cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of 5×10^5 cells/ml. Plate 200 ul cells per well in the 96-well plate (or 1×10^5 cells/well).

- 20 Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at 37°C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.

Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.

- 25 When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor).

- 5 The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene
10 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified
15 product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30
20 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-
25 inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine
30 protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine

growth-but-every-one-to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS
5 (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as 5×10^5
10 cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to 1×10^5 cells/well). Add 50 ul supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold
15 induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

Example 16: High-Throughput Screening Assay for T-cell Activity

NF- κ B (Nuclear Factor κ B) is a transcription factor activated by a wide
20 variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF- κ B regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- κ B appears to shield cells from apoptosis), B and T-cell development,
25 anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- κ B is retained in the cytoplasm with I- κ B (Inhibitor κ B). However, upon stimulation, I- κ B is phosphorylated and degraded, causing NF- κ B to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- κ B include IL-2, IL-6, GM-CSF, ICAM-1 and
30 class I MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF- κ B promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF- κ B would be useful in treating diseases. For example, inhibitors of NF- κ B could be used to treat those diseases related to the acute or chronic activation of NF- κ B, such as rheumatoid arthritis.

To construct a vector containing the NF- κ B promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF- κ B binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGAC
TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCC
ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCC
ATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGA
CTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGCCTCTGAGCTA
TTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAA
GCTT:3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2- promoter plasmid (Clontech) with this NF- κ B/SV40 fragment using XhoI and

~~HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.~~

In order to generate stable mammalian cell lines, the NF- κ B/SV40/SEAP cassette is removed from the above NF- κ B/SEAP vector using restriction enzymes
5 SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF- κ B/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF- κ B/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly,
10 the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 13. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 17: Assay for SEAP Activity

15 As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 μ l of 2.5x
20 dilution buffer into Optiplates containing 35 μ l of a supernatant. Seal the plates with a plastic sealer and incubate at 65°C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 μ l Assay Buffer and incubate at room
25 temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 μ l Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

30 Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 18: High-Throughput Screening Assay Identifying Changes in Small**5 Molecule Concentration and Membrane Permeability**

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants

which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

5 The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

10 For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO₂ incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

 A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To
15 load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37°C in a CO₂ incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

 For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10⁶ cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml
20 fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37°C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10⁶ cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed
25 once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

 For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4. The supernatant is added to the well, and a change in fluorescence is detected.

 To measure the fluorescence of intracellular calcium, the FLIPR is set for the
30 following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm;

and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular Ca^{++} concentration.

5 **Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity**

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St.

~~Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or~~
calf serum, rinsed with PBS and stored at 4°C. Cell growth on these plates is assayed
by seeding 5,000 cells/well in growth medium and indirect quantitation of cell
number through use of alamarBlue as described by the manufacturer Alamar
5 Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from
Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen
Plates. Falcon Microtest III cell culture plates can also be used in some proliferation
experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of
10 Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium.
Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20
minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in
Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM
HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na₃VO₄, 2 mM
15 Na₄P₂O₇ and a cocktail of protease inhibitors (# 1836170) obtained from
Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is
shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a
vacuum transfer manifold and the extract filtered through the 0.45 mm membrane
bottoms of each well using house vacuum. Extracts are collected in a 96-well
20 catch/assay plate in the bottom of the vacuum manifold and immediately placed on
ice. To obtain extracts clarified by centrifugation, the content of each well, after
detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at
4°C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many
25 methods of detecting tyrosine kinase activity are known, one method is described
here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by
determining its ability to phosphorylate a tyrosine residue on a specific substrate (a
biotinylated peptide). Biotinylated peptides that can be used for this purpose include
30 PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and

PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg₂⁺ (5mM

- 5 ATP/50mM MgCl₂), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl₂, 5 mM MnCl₂, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30°C for 2 min. Initiate the reaction by adding 10ul of the control enzyme or the filtered supernatant.

- 10 The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37°C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide.

- 15 Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37°C for one hour. Wash the well as above.

- 20 Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

25 **Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity**

- As a potential alternative and/or complement to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine
- 30

phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1-hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against

Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4°C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place

of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

Example 21: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky, D., et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton, T.A. and Graham, M.W., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson, Cg. et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson, Cv.

et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

10 A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

15 For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to
20 the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

25 Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

30 Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard

curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

5

Example 23: Formulating a Polypeptide

The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1 $\mu\text{g/kg/day}$ to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day , and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1 $\mu\text{g/kg/hour}$ to about 50 $\mu\text{g/kg/hour}$, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and R. Langer, Chem. Tech. 12:98-105 (1982)); ethylene-vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's

solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical

compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the
5 polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

Example 24: Method of Treating Decreased Levels of the Polypeptide

It will be appreciated that conditions caused by a decrease in the standard or
10 normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to
15 increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

20

Example 25: Method of Treating Increased Levels of the Polypeptide

Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as
25 cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense
30 polynucleotide is provided in Example 23.

Example 26: Method of Treatment Using Gene Therapy

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector.

The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 27: Method of Treatment Using Gene Therapy - In Vivo

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata H. et al. (1997) Cardiovasc. Res. 35(3):470-479, Chao J et al. (1997) Pharmacol. Res. 35(6):517-522, Wolff J.A. (1997) Neuromuscul. Disord. 7(5):314-318, Schwartz B. et al. (1996) Gene Ther. 3(5):405-411, Tsurumi Y. et al. (1996) Circulation 94(12):3281-3290 (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection

into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that 5 quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be used to extrapolate proper dosages and other treatment parameters in humans and other animals using naked 10 DNA.

Example 28: Transgenic Animals.

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, 15 guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e.g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

20 Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology 25 (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the 30 polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-

mediated-gene-transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones
5 containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene
10 in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et
15 al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is
20 to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only
25 that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the
30 recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA

expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also
5 be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more
10 than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for
15 screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not
20 limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

25 **Example 29: Knock-Out Animals.**

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson et al., *Cell* 5:313-321 (1989); each of which is incorporated by
30 reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding

regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e.g., see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and
5 Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For
10 example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological
15 function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

It will be clear that the invention may be practiced otherwise than as
20 particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other
25 disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule-13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>178</u> . line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country): <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>May 18, 1998</u>	Accession Number <u>209878</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") 	

For receiving Office use only	
<input checked="" type="checkbox"/> This sheet was received with the international application	
Authorized officer	<u>Mary Walker</u> <u>International Division</u> <u>703-261-2332</u> <u>mailto:walker@uspto.gov</u>

For International Bureau use only	
<input type="checkbox"/> This sheet was received by the International Bureau on:	
Authorized officer	

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

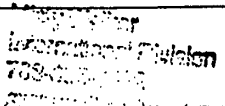
(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>179</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit February 26, 1997	Accession Number 97898
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	
For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer Misty Walker International Division TCS-SIS-0032 mailto:mwalker@uspto.gov	Authorized officer

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT-Rule-13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>179</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>May 15, 1997</u>	Accession Number <u>209044</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") 	

For receiving Office use only	
<input checked="" type="checkbox"/> This sheet was received with the international application	
Authorized officer 	

For International Bureau use only	
<input type="checkbox"/> This sheet was received by the International Bureau on:	
Authorized officer	

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>179</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit August 28, 1997	Accession Number 209225
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	
<input checked="" type="checkbox"/> This sheet was received with the international application	
Authorized officer	<i>[Signature]</i> International Division 700-615-2000

For International Bureau use only	
<input type="checkbox"/> This sheet was received by the International Bureau on:	
Authorized officer	

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>180</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit March 7, 1997	Accession Number 97923
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	
<input checked="" type="checkbox"/> This sheet was received with the international application	
Authorized officer <u>M. Walker</u> <u>International Division</u> <u>7CS-605-0000</u>	

For International Bureau use only	
<input type="checkbox"/> This sheet was received by the International Bureau on:	
Authorized officer	

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>180</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit May 22, 1997	Accession Number 209071
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	
<div>For receiving Office use only</div> <div><input checked="" type="checkbox"/> This sheet was received with the international application</div> <div>Authorized officer Patricia J. Schell International Division 703-495-0932 microbaillet@uspto.gov</div>	<div>For International Bureau use only</div> <div><input type="checkbox"/> This sheet was received by the International Bureau on:</div> <div>Authorized officer</div>

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT-Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>180</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>February 12, 1998</u>	Accession Number <u>209626</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") 	
For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application Authorized officer: <u>Michael Nether</u> <u>International Division</u> <u>703-602-6682</u>	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer: _____

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT-Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>181</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit March 20, 1998	Accession Number 209683
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	
For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer [Signature] 708-433-0000	Authorized officer

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>181</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>February 25, 1998</u>	Accession Number <u>209641</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	
For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer <u>John J. ...</u> <u>...</u> <u>...</u>	Authorized officer <u>...</u>

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT-Rule.13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>181</u> . line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit July 9, 1997	Accession Number 209141
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	
<div>For receiving Office use only</div> <div><input checked="" type="checkbox"/> This sheet was received with the international application</div> <div>Authorized officer [Signature] [Stamp]</div>	<div>For International Bureau use only</div> <div><input type="checkbox"/> This sheet was received by the International Bureau on:</div> <div>Authorized officer</div>

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>181</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>February 26, 1997</u>	Accession Number <u>97901</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") 	
For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application Authorized officer <u>[Signature]</u> <u>Division</u>	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer _____

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>181</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>May 15, 1997</u>	Accession Number <u>209047</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") 	
For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application Authorized officer <u>[Signature]</u>	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer _____

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>181</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>May 18, 1998</u>	Accession Number <u>209877</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") 	
For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application Authorized officer <u>Sally Walker</u> <u>International Division</u> <u>703-605-6832</u>	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer _____

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT-Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>182</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT	
Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>January 14, 1998</u>	Accession Number <u>209580</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable)	
This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	
For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT-Rule-13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>185</u> , line <u>N/A</u>	
Further deposits are identified on an additional sheet <input type="checkbox"/>	
B. IDENTIFICATION OF DEPOSIT	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>May 22, 1998</u>	Accession Number <u>209889</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	
For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application Authorized officer <u>[Signature]</u>	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer

What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:
- 5 (a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
 - (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a
10 polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
 - (c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
 - 15 (d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
 - (e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X,
20 having biological activity;
 - (f) a polynucleotide which is a variant of SEQ ID NO:X;
 - (g) a polynucleotide which is an allelic variant of SEQ ID NO:X;
 - (h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;
 - 25 (i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.

5 3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

10 4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

15 5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

20 6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

25 7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

30 9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.

-
11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:
- (a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
 - 5 (b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;
 - (c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
 - 10 (d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
 - (e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
 - (f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
 - 15 (g) a variant of SEQ ID NO:Y;
 - (h) an allelic variant of SEQ ID NO:Y; or
 - (i) a species homologue of the SEQ ID NO:Y.
12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.
- 20
13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.
- 25
14. A recombinant host cell that expresses the isolated polypeptide of claim 11.
15. A method of making an isolated polypeptide comprising:
- (a) culturing the recombinant host cell of claim 14 under conditions such that
 - 30 said polypeptide is expressed; and
 - (b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

- (a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and
- (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

- (a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and
- (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

- (a) contacting the polypeptide of claim 11 with a binding partner; and
- (b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay, wherein the method comprises:

- (a) expressing SEQ ID NO:X in a cell;
- (b) isolating the supernatant;

-
- ~~(c) detecting an activity in a biological assay; and~~
 - (d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

1

Sequence Listing

<110> Human Genome Sciences, Inc., et al.

<120> 71 Human Secreted Proteins

<130> PZ030PCT

<140> Unassigned

<141> 1999-07-14

<150> 60/092,956

<151> 1998-07-15

<150> 60/092,921

<151> 1998-07-15

<150> 60/092,922

<151> 1998-07-15

<160> 262

<170> PatentIn Ver. 2.0

<210> 1

<211> 733

<212> DNA

<213> Homo sapiens

<400> 1

gggatccgga	gcccaaattct	tctgacaaaa	ctcacacatg	cccaccgtgc	ccagcacctg	60
aattcgaggg	tgaccgtca	gtcttcctct	tcccccaaa	acccaaggac	accctcatga	120
tctcccgga	tcctgaggtc	acatgcgtgg	tggtggacgt	aagccacgaa	gacctgagg	180
tcaagttcaa	ctggtacgtg	gacggcgtgg	aggtgcataa	tgccaagaca	aagccgctgg	240
aggagcagta	caacagcacg	taccgtgtgg	tcagcgtcct	caccgtcctg	caccaggact	300
ggctgaatgg	caaggagtac	aagtgaagg	tctccaacaa	agcctccca	accccatcg	360
agaaaaccat	ctccaaagcc	aaagggcagc	ccgagaacc	acaggtgtac	accctgcccc	420
catcccggga	tgagctgacc	aagaaccagg	tcagcctgac	ctgcctggtc	aaaggcttct	480
atccaagcga	catcgccgtg	gagtgggaga	gcaatgggca	gccgggagaac	aactacaaga	540
ccacgcctcc	cgtgctggac	tccgacggct	ccttcttcct	ctacagcaag	ctcaccgtgg	600
acaagagcag	gtggcagcag	gggaacgtct	tctcatgctc	cgtgatgcat	gaggctctgc	660
acaaccacta	cacgcagaag	agcctctccc	tgtctccggg	taaagagtg	cgacggccgc	720
gactctagag	gat					733

<210> 2

<211> 5

<212> PRT

<213> Homo sapiens

<220>

<221> Site

<222> (3)

<223> Xaa equals any of the twenty naturally occurring L-amino acids

<400> 2

Trp Ser Xaa Trp Ser

1

5

<210> 3
<211> 86
<212> DNA
<213> Homo sapiens

<400> 3
gcgcctcgag atttccccga aatctagatt tccccgaaat gatttccccg aaatgatttc 60
cccgaatat ctgccatctc aattag 86

<210> 4
<211> 27
<212> DNA
<213> Homo sapiens

<400> 4
gcggcaagct ttttgcaaag cctaggc 27

<210> 5
<211> 271
<212> DNA
<213> Homo sapiens

<400> 5
ctcgagattt ccccgaaatc tagatttccc cgaaatgatt tccccgaaat gatttccccg 60
aaatatctgc catctcaatt agtcagcaac catagtcccg ccctaactc cgcccatccc 120
gcccctaact ccgcccagtt ccgcccattc tccgcccacat ggctgactaa ttttttttat 180
ttatgcagag gccgaggccg cctcggcctc tgagctattc cagaagtagt gaggaggcctt 240
ttttgaggc ctaggctttt gcaaaaagct t 271

<210> 6
<211> 32
<212> DNA
<213> Homo sapiens

<400> 6
gcgctcgagg gatgacagcg atagaacccc gg 32

<210> 7
<211> 31
<212> DNA
<213> Homo sapiens

<400> 7
gcgaagcttc gcgactcccc ggatccgcct c 31

<210> 8
<211> 12
<212> DNA
<213> Homo sapiens

<400> 8
ggggactttc cc 12

<210> 9

<211> 73

<212> DNA

<213> Homo sapiens

<400> 9

gcggcctcga ggggactttc ccggggactt tccggggact ttccgggact ttccatcctg	60
ccatctcaat tag	73

<210> 10

<211> 256

<212> DNA

<213> Homo sapiens

<400> 10

ctcgagggga ctttcccgga gactttccgg ggactttccg ggactttcca tctgccatct	60
caattagtca gcaaccatag tcccggccct aactccgccc atcccggccc taactccgcc	120
cagttccgcc cattctccgc cccatggctg actaatTTTT tttatttatg cagagggcca	180
ggccgcctcg gcctctgagc tattccagaa gtagttagga ggcttttttg gaggcctagg	240
cttttgcaaa aagctt	256

<210> 11

<211> 1113

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (393)

<223> n equals a,t,g, or c

<400> 11

gatgctcctt tagcttgagg gagtttggtta ttaccacact tctgaagcct acttctgtca	60
attcatccaa ctcatctctca gtccagtttt gtttccttgc tggtagaggag ttgtgaccc	120
ttggaggaga agaggcattc tgggttttgg aatttttagc cattttgtctc tggtttcttc	180
ccatctttgt ggatttatct acctttcatc ttcaatgtta gtgacctatg gatggggctct	240
ctgagtggaat gtgctcttcc tttctgtttg twagttttct ttctaacagt tagccccctct	300
gctgtaggtc tgctggaktt tgctggaggt cactccaga ccctgtttgc ctgggtatca	360
ccagtggagg ctgcagaaca gcaaagattg ctncctgttc tttcctctgg aagcttcgtc	420
tcagagggca cctgccagat gccagccaga gctctcctgt atgaggtgtc tgttggcca	480
tactgggaga ttcctcccag tcaggatata aggaggtcag ggacctactt gaggaggcag	540
tctgaccctt agcagagggt gaacactgtg ctaggaggtc ctctgtctctt ttcagagctg	600
tcaggcgggg cgtataagtc tgctgaatct gtgtccgcag ccacctctc cccaggtgc	660
tctgtcccag ggagatgggg gttttatttt taagtcccca actggggctg ctgccttttt	720
ttcagagatg ccctgcccag agaggagaaa tctggcagtc tggcctcaga ggccttgctg	780
agctgccgtt ggctccaccc agttcaaaact tcccaagggg ctttgtttat actgtaaggg	840
gaaaaccgcc tactcgagcc tcatcaatgg cagacacccc tcccgcgcc aagcttaagt	900
gtcccaggtt gatctcagac tgctgctgtg ctggcagtga gaatttcaag ccagtggatc	960
ttagtttgct gtgctctgtg ggggtgggac ccattgaacc agactactcg gctccctggc	1020
ttcagccccc tttccaggag agtgaagggt tctgtctcat tggcattcca ggagtcactg	1080
gtgtatggaa aaaaaaaaaa aaagggcggc cgc	1113

<210> 12

<211> 983
 <212> DNA
 <213> Homo sapiens

<400> 12

ggcacgaggg	cagctgcaga	gctccagggt	tctctgcca	caagggcagg	ggctgccct	60
cgccaggat	gactctgct	tccagagcct	tgccctccct	gggggtggga	gtgtggggga	120
tgctaagggt	aaatcagggt	acagtaagtt	gtgggggcag	cagggtggagc	agcagagtgg	180
cactgggagc	tttctcttg	gtgtgcgggt	tgcccttggt	tctgcagcca	tcagggtggg	240
gcttgggact	gacttctcct	tctgaaggat	gctggggaag	tgagctggct	ttggcagtgc	300
ttagagctcc	gggggggtcc	ccctcctaga	acatgcaagc	tctcacaccg	gtgcgtcatc	360
atcacacca	tcatcaagcc	cacagtggta	tactgaacac	ctgcccaca	aagacggtgg	420
actgctctca	gaggagcccc	atgaaccacc	gatggttaca	actatccaat	gcctgatggc	480
agacagccag	gccaacctcg	gcttccactc	tctcttcttc	accctacaat	cagccaaagt	540
gacctgagtc	atgtagtgtg	aagttgcttt	ctgctttctc	ttgtttgtgc	ttttgctgtt	600
tcttctgccc	catactttgt	taactccatg	agttaaatgc	taccattttt	cccagacaag	660
tgctgcttct	gcaaggaaac	ccttctctgat	ccccaccta	tctgaaaagt	acctctccag	720
cttgcttctt	cagggtgctg	agcgttcctt	cccagcctgt	catcaccttc	ctccatacgc	780
tatggtgtgt	tcctgtcttc	tctagtcttg	tcctcttttt	tctgttagat	tgtagctcct	840
tgctgacagg	aaccacgcct	gctccagctt	catacctccc	actgctacag	cacagaacct	900
gcttctcaga	cttacagcaa	atgtttgttt	gctgaatgaa	ttaattaaag	ataaagcaaa	960
aaaaaaaaaa	aaaaaaactc	gag				983

<210> 13
 <211> 973
 <212> DNA
 <213> Homo sapiens

<400> 13

ggcacgagcc	cagcggaagc	caagccacca	ggccccccag	cgccacgcg	gagcatgaac	60
attgaggatg	gcgctgccc	gcggctcccc	gtgccccccg	ctgccgccc	gtaggatgtc	120
ctggccccac	ggggcattgc	tcttctctct	gctcttctcc	ccacccttg	gggcccgtgg	180
aggtggagtg	gccgtgacgt	ctgccgcgg	agggggctcc	ccgccggcca	cctcctgccc	240
cgtggcctgc	tcctgcagca	accaggccag	ccgggtgatc	tgcacacgga	gagacctggc	300
cgaggtccca	gccagcatcc	cgggtcaacac	gcggtacctg	aacctgcaa	agaacggcat	360
ccaggtgatc	cggacggaca	cgttcaagca	cctgcggcac	ctggagattc	tgtagctgag	420
caagaacctg	gtgcgcaaga	tcgaggtggg	gccttcaac	gggctgcca	gcctcaacac	480
gctggagctt	tttgacaacc	ggctgaccac	ggtgcccacg	caggccttcg	agtagctgtc	540
caagctgcgg	gagctctggc	tgcggaacaa	ccccatcgag	agcatcccct	cctacgcctt	600
caaccgcgtg	ccctcgctgc	ggcgctgga	cctgggcgag	ctcaagcggc	tggaatacat	660
ctcggaggcg	gccttcgagg	ggctggtcaa	cctgcgctac	ctcaacctgg	gcatgtgcaa	720
cctcaaggac	atccccaac	tgacggccct	ggtgcgcctg	gaggagctgg	agctgtcggg	780
caaccggctg	gacctgatcc	gcccgggctc	cttccagggt	ctcaccagcc	tgcgcaagct	840
gtggctcatg	cacgcccagg	tagccaccat	cgagcgcaac	gccttcgacg	acctcaagtc	900
gctggaggag	ctcaacctgt	cccacaacaa	cctgatgtcg	ctgccccacg	acctcttcac	960
gccctgcac	cgc					973

<210> 14
 <211> 1458
 <212> DNA
 <213> Homo sapiens

<400> 14

ccacgcgtcc	gggaattttc	aaaagatcca	aacagagact	tcctgcatct	tctgcctttc	60
caacagaagc	ggtgatcgtc	taagtatgag	cctgtggctt	cctttgtgca	tttgagcatg	120
ctgtaattaa	gatgagatca	gtttcttaga	aaaagctttc	ctgaatccct	ctgacgttgc	180

ctgggatctt	tctgttgatt	cgtcttttct	ggagattggg	acagagcatc	tgtggtccag	240
ggaagttagt	cctctggcct	caattctgtt	gtggatgtgc	agtgataagc	gggcattgcg	300
tgcctcgggg	gatgcctagt	tcgtggcttc	ctggctgttt	tgctcttctg	tgctctgtag	360
ctgtagggtg	ccagctcagg	gagtggggtg	ttggcggcgt	ttccgcgggt	ggcctccttg	420
ctttgccgca	cctccagggt	ctgggcatga	gaggccgtgg	cctcatttct	ggtggataac	480
cttttttagt	taatagcatc	tttaattaga	tcacagcatt	gaattcaaaa	tttcttctgc	540
aaagaaagt	gtggggcata	agacaccggg	aatgaggggag	gaggaagaca	gttgtgtttt	600
ctcttttaac	cttgagctct	agccgatgca	tttgtcagga	aatacagcac	tttgtcttaa	660
gaaaacaagg	aaggaggccg	ggcgagtggt	ctcacgcctg	taatcccagc	actttgggag	720
gccgaggcgg	gcggtatcac	tgagggtggg	agtatgagac	caccctgact	aacatggaga	780
gaccctgtct	ctactaaaag	tacagaatta	gccgggctgt	gttgcgcatg	cccataatcc	840
cagctactga	ggagacttga	ggtaggagaa	tcacttgaac	ctcagcggcg	gaggttgtag	900
tgagtcgaga	tcgcgccagt	gcactccagc	ctgggcaaga	agagcgaaac	tgggtctcaa	960
gttaaaaaaa	gaaagcaagg	aaagagtaat	ttacaacgaa	ggaaaaaaac	ccacagcaca	1020
cccttcgcgg	ctgtcagcgc	tctcctgatg	tcacagtggc	tgcgtgtcct	tgggtgtggg	1080
gaggtgtggg	gagcccagcc	cctggccctg	cctccgcgcg	cccgtctccc	ttctctctct	1140
tactcgggta	agccatagcg	aggcctccgc	tcgtttcaga	tatgaatttg	ttttatagat	1200
tataaatatg	catatacagt	gtatgtataa	agcagaatgc	ctgcctttcc	tggttatttt	1260
ttgtaccata	ttgtaaatga	tattatttat	tctttaccaa	ttttgggaat	aaaagggtgt	1320
ttggttattt	aataataata	gagctgttaa	acttctgttt	aaatttccag	ttcaacttgt	1380
aaatgttttt	attgtgcata	aatacatact	aatgttgatc	taaaaaaaaa	aaaaaaaaaa	1440
aaaaaaaaaa	aaaaaaaaaa					1458

<210> 15

<211> 2005

<212> DNA

<213> Homo sapiens

<400> 15

ggttgctggc	ccagggtgagc	ggggcgcgctg	gtccagggtga	gcggggcgcg	ccccgcgacg	60
gcgctgcctg	cccagaggcgg	ttcacgtaaa	gacagcgaga	tcctgagggc	cagccgggaa	120
ggaggcggtg	atatggagct	ggctgctgcc	aagtccgggg	cccgcgccgc	tgcctagcgc	180
gtcctgggga	ctctgtgggg	acgcgccccg	cgccgcggct	cggggaccgc	tagagcccg	240
cgctgcgcgc	atggccctgc	tctcgcgccc	cgcgctcacc	ctcctgtctc	tcctcatggc	300
cgctgttgtc	aggtgccagg	agcaggccca	gaccaccgac	tggagagcca	ccctgaagac	360
catccggaac	ggcgttcata	agatagacac	gtacctgaac	gccgccttgg	acctcctggg	420
aggcgaggac	ggctctctgc	agtataaatg	cagtgcgga	tctaagcctt	tcccacgtta	480
tggttataaa	ccctccccac	cgaatggatg	tggctctcca	ctgtttgggt	ktcatcttaa	540
cattggtatc	ccttccctga	caaagtgttg	caaccaacac	gacagggtgt	atgaracctg	600
tggcaaaagc	aagaatgact	gtgatgaaga	attccagtat	tgctctcca	agatctgccg	660
agatgtacag	aaaacactag	gactaactca	gcatgttcag	gcatgtgaaa	caacagtgga	720
gctcttggtt	gacagtgtta	tacatttagg	ttgtaaacca	tatctggaca	gccaacgagc	780
cgcatgcagg	tgctattatg	aagaaaaaac	tgactcttaa	aggagatgcc	gacagctagt	840
gacagatgaa	gatggaagaa	cataaccttt	gacaaataac	taatgttttt	acaacataaa	900
actgtcttat	ttttgtgaaa	ggattatttt	gagaccttaa	aataatttat	atctttagat	960
taaaacctca	aagcaaaaaa	agtgaggggag	atagtgaggg	gagggcacgc	ttgtcttctc	1020
aggatatctt	cccagcattg	ctcccttact	tagtatgcc	aatgtcttga	ccaatatcaa	1080
aaacaagtgc	ttgttttagcg	gagaattttg	aaaagaggaa	tataataact	aattttcaca	1140
accacattta	ccaaaaaaag	agatcaaata	taaaattcat	cataatgtct	gttcaacatt	1200
atcttatatt	gaaaatgggg	aaattatcac	ttacaagtat	ttgtttacta	tgaaatttta	1260
aatacacatt	tatgcctaga	aggaacggac	tttttttttc	tatttttaatt	acacataata	1320
tgaatataaa	gtmcaacata	atatgttggt	tctctgtagc	ccgttgagca	tatgagtaag	1380
tcacatttct	attaggacta	cttmcaagga	caagggtttc	atttttccag	ttgtaaaatt	1440
ggaaccatca	gctgataacc	tcgtaggggag	caaccccgag	atagctaagt	gttatgtaat	1500
atgcctagaa	ggtgatgtga	atgcgattca	gaagcatagc	cactcccat	ttatgagcta	1560
ctcacatgac	aaatgtcatc	ttttgtcata	acctttgcca	agttagagaa	aagatggatt	1620
taatgagata	aatgaaaaga	tatttamcct	aatatatcaa	ggcactattt	gctgttatgc	1680

tttgttattt	atttcccagc	acttgttcct	tattgtagat	tttttaaaga	ctgtaacctt	1740
ttactaactg	tggctcttact	aaaatttgtg	cttgatactg	cttttcaaaa	agcctttaat	1800
tagagccaaa	aggatggaaa	aggcaagata	taaatgcctt	ttatagatct	cttatttaca	1860
ttgaaaatta	ttaccatatg	tttagagcaa	atccaagaaa	acttcaacag	cttctgaaga	1920
tgctctatgaa	tgttgaaaac	ttttcaatst	cttggratgc	tcakttaatt	cgcagaccgg	1980
cttaacggat	taaacgcccc	cccc				2005

<210> 16

<211> 943

<212> DNA

<213> Homo sapiens

<400> 16

ggcagagct	ccgcccggcc	ccgaggggct	ctccccggag	gctcagcccc	ctctgctccc	60
catgggcaac	tgccaggcag	ggcacaacct	gcacctgtgt	ctggcccacc	acccacctct	120
ggtctgtgcc	actttgatcc	tgctgctcct	tggcctctct	ggcctgggcc	ttggcagctt	180
cctcctcacc	cacaggactg	gectgcgcac	cctgacatcc	cccaggactg	ggtctctttt	240
ttgagatctt	ttggccagct	gaccctgtgt	cccaggaatg	ggacagtcac	agggaaagtgg	300
cgaggggtctc	acgtcgtggg	cttgctgacc	accttgaact	tcggagacgg	tccagacagg	360
aacaagacct	ggacattcca	ggccacagtc	ctgggaagtc	agatgggatt	gaaaggatct	420
tctgcaggac	aactggctct	tatcacagcc	aggggtacca	cagaaaggac	tgcaggaacc	480
tgctctatatt	ttagtgctgt	tccaggaatc	ctacctcca	gccagccacc	catatcctgc	540
tcagaggagg	gggctggaaa	tgccaccctg	agccctagaa	tgggtgagga	atgtgttagt	600
gtctggagcc	atgaaggcct	tgtgctgacc	aagctgctca	cctcggagga	gctggctctg	660
tgtggctcca	ggctgctggt	cttgggctcc	ttcctgcttc	tcttctgtgg	ccttctctgc	720
tgtgtcactg	ctatgtgctt	ccaccgcgcg	cgggagctcc	actggtctag	aaccggctc	780
tgagggcact	ggcctagtct	ccgacttggt	tctcaggtgt	gaatcaactt	cttgggcctt	840
ggctctgagt	tggaaaaggt	tttagaaaaa	gtgaagagct	ggaatgtggg	ggaaaataaa	900
aagctttttt	gccccaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaa		943

<210> 17

<211> 1503

<212> DNA

<213> Homo sapiens

<400> 17

caggttcctc	tcagtamarc	ctcarsecga	ggttcccttc	ctcttgcatc	catgtgtgtg	60
tttcaraggc	ggccatcctt	ccctacttcc	agatccttgt	agggcagttg	gtggaggggtg	120
ggaggcacc	cggtgttgcc	tccatgaagc	cctgtgcccag	tactgggct	gcaaggctga	180
ggaaattgtg	tccgtgtcag	aaagctcctc	agctcagagg	tgctggtagc	tcctgctgtg	240
taggaaggca	gggggaagag	gccctgcttc	tctgtttctc	tttgccctta	tgagacttga	300
gagtcgtgtg	catctgtgcc	ttgcatgtct	ttttttcaga	ctccctgcga	caaggactgt	360
gtactgcatg	aatgaggctg	agatagttag	tgttgctctg	ggaatcctga	ttgagagccg	420
yaaacaggam	aaggcctgcy	agcagccggc	cctggcgggg	gctgataacc	cagagcactc	480
ccctccctgc	tccgtgtcgc	ctcacacaag	ttctgggagc	agcagtgagg	aagaggacag	540
tgggaaacag	gcactgrctc	caggcctcag	cccttcccag	aggccggggg	gttccagctc	600
tgctgttagc	aggagccctg	aggaggagga	ggaagaggat	gtgctgaaat	acgtccggga	660
gatctttttc	agctagggca	taaaactgtg	actgaactgt	ctgccgagag	cagctggagg	720
acagctgagc	ttccactggg	gctgctgggc	cgcccgcctg	tgggaatggg	gctctctgtg	780
ctcctacctt	tgtgccttct	tgggcctggc	agattcacct	caggccagaa	gcccctggac	840
actccgggct	ttggggctgc	cgttctgagt	gtgcggaagg	caggactcaa	aatgagatcc	900
catttgactc	cctctgtatg	tactgtgccc	tctcctggct	cttgaggctc	tggagtccca	960
attgtctgtg	ttagtcagtg	accaggttcc	agggaaaatg	atgtcatgtg	gtggtccaac	1020
ttactggaac	caaagagaca	gtactttgca	aagaaaagga	tactgcccag	gtgactgga	1080
attgctacag	tttagtccgc	atgatctctc	ctgaaggagg	aagcctgttt	caaaaatagt	1140
ttccatcatg	agtctatcaa	tgagctccca	cctctccagc	cagcctagaa	agcaaacgag	1200

ctgcccacag	ttctctgccc	tgtctgggag	gttgaggcca	cagtgtatag	actggtaagc	1260
cagacaggcc	tctctccgca	agctgctacc	ttgctttcac	ctgtacctg	gtccccgggc	1320
agctagctat	aaagcaagag	ggacaggagc	ccagaagaga	cactgaggac	aagagatcac	1380
accagagtac	atgtctctgc	ctctgttttc	agtgtggctt	tggaacaggaa	tatatgaata	1440
aatcactgcc	atacaggttt	tccaatacac	aagtgctaga	aaatacacac	aattccccaa	1500
tga						1503

<210> 18
 <211> 1512
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (207)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (209)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (521)
 <223> n equals a,t,g, or c

<400> 18	
gcagagcccc	tggtgtgag aagctcgtct cccgtgggtt gcattggctc tgccctatct 60
ctgcctccag	caccagggc ggccgcagat ggcagtgtct ctggggacag cagctgcgaa 120
tgagtccacg	ggccaacgct gagctgtctc ggctgaggcg gtgtgtctcag cacagagccc 180
ccggaactgg	catctgcagg gcgtgancna aggccgccgc gatgccgcac ttcctggact 240
ggttcgtgcc	ggtctacttg gtcactctcg tctcattctt ggtgggcttc ggccgctgca 300
tctactactt	cgagccgggc ctgcaggagg cgcacaagtg gcgcatgcag cggcccttgg 360
tggaccgcsa	cctccgcaag acgctaattg tgcgcgacaa cctggccttc ggccggcccg 420
aggtctgagc	cgacttgcaa aggggatagg csgggcgcac cgggcgcctt ccccgagccc 480
gccccgcccc	cccagcccgg agaccccaa ggcagaggga ngccggcctg ttggccctcc 540
acgctatccc	tctgcagcct gggccctccc gacagaggcc ccaggtgcgc tgscagtgra 600
gggtggggcac	ttaggtgect ggctggccca gggcttgctc tccgtgtcaa gccgactcac 660
ccagagccca	ccctcccaag ctccagggga tctccgctg ggccccagt cctttgcrct 720
gcgcagcact	ctgccctcca ctggactcag gcatgtctat ggctgcctgt cctgaggctc 780
cggagccctc	atttcttcgt gaagtcccca gctcccctgc ctccactcaa tggcaccggc 840
cctgcaactt	taggcaggtc gaagccaacc caaggaaaga acctaagaac ctctgttggg 900
gggatgtcag	cttggggccag mcccagccga ccccgcgggg ctgaggcttg gaactggtga 960
gggtgtgtgg	tggggggtatg cagagggata agaccgtggt agaggagagg gttggtgagg 1020
agagagagag	agagagagag agagagagtc tggggggagc gggcaagcat ggggagatga 1080
gatgtgtata	tgtgagagag agtgtggggg cccagggcag ggcaggaggt ggtggaaacg 1140
gggtgaactc	cgtgggctgt gtgaggactg tccatagtgg gtccmaaccc cctccctctg 1200
ctggagtttc	ctagcccttc cccctcccyg agactgwggc agcaggcagg agcccctgcc 1260
ctccctccct	gtcctgtgcc acacttctgg ggccaaaccc agcccccttg agccaggccc 1320
tgccagactc	caagcccacc ctagaacctt cctcctgtgt ggagactctg ttgccccact 1380
ttggacacag	atttgcaacc tgccctaccm ckccccctw cgctgggggt tccatcttaa 1440
tttattctca	ataataaaga cttcatgatg amaaaaaaa aaaaaaaaaa aaaaaaaaaa 1500
aaaaaaaaaa	aa 1512

<210> 19

<211> 1655
<212> DNA
<213> Homo sapiens

<400> 19
ccacgcgtcc gggcaaagaa ttaaacctgg tgtttggact tcaacttagc atggctagaa 60
ttggaagtac agtaaacaatg aacctcatgg gatggctgta ttctaagatt gaagctttgt 120
taggttctgc tggtcacaca accctcgga tcacacttat gattgggggt ataactgtgta 180
ttctttcact aatctgtgcc ttggctcttg cctacttggg tcagagagca gagagaatcc 240
ttcataaaga acaaggaaaa acaggtgaag ttattaaatt aactgatgta aaggacttct 300
ccttaccctt gtggcttata tttatcatct gtgtctgcta ttatgttgct gtgttccctt 360
ttattggact tgggaaagt ttctttacag agaaatttg attttcttcc caggcagcaa 420
gtgcaattaa cagtgttgta tatgtcatat cagctcccat gtccccgtg tttgggctcc 480
tggtggataa aacagggaag aacatcatct gggttctttg cgcatagcag ccactcttgt 540
gtccacatg atgctggcct ttacgatgtg gaacccttg attgctatgt gtcttctggg 600
actctcctac tcattgcttg cctgtgcatt gtggccaatg gtggcatttg tagttcctga 660
acatcagctg ggaactgcat atggcttcat gcagtcatt cagaatcttg ggttggccat 720
catttccatc attgctggtg tgatactgga ttctcggggg tatttgtttt tgggaagtgtt 780
cttcattgcc tgtgtttctt tgtcactttt atctgtggtc ttactctatt ggtgaatcgt 840
gcccagggtg ggaacctaaa ttattctgca agacaaagga agaaataaaa tttcccatac 900
tgaatgagaa gttaaaatga atgtgtcaga gaatgggctt aacacatcgt tggtttgaaa 960
acttccattt taaaaattta gagtttagtc attagaaaaa ataatggact ggaaagtat 1020
atztatatcc aaatatacct atttcaaagt gtatttgtga ggcctgtttt agcctgtgtc 1080
ttttgtattg tgtgttgcta aagaattcta cttttagtag gctaataaac aatgaaaggg 1140
ttagaaaatt gctgtggaac atccagggtg acttcaggaa agacagtga aaatggaaaa 1200
cgttggagct tctgttgaga taatcttcat taggtatata tcttagggat acagcctttt 1260
ctttatctta tagcaggaaa aaaaaacttt tgagggaaat agaagggctg cgttacacaa 1320
aataaacaat ggcattgtca taggccttcc ttttactagt agggcataat gctagggaat 1380
atgtgaagat gtttttttga agtctcttcc tgatcacgaa caatagcttg cgctctactc 1440
tgtagttatg tggattgccg agcaatgacc cttttcaatt tcttatttct gtgttactga 1500
ggacccta at cacttaggga tgtaatttta tagtataaac tttctgtaca gtttttctta 1560
tagtctaata agtaaaaagt gtccttcaaa ttatgataat tgcctatgta catggataaa 1620
ttaaaacact gcacacggaa aaaaaaaaaa aaaaaa 1655

<210> 20
<211> 2525
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (5)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (10)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1354)
<223> n equals a,t,g, or c

<400> 20
tgacnctatn gtaagggtacg cctgcaggta ccggtccgga attccccgggt cgaccacgc 60
gtccgggtctg ccaacaaggt cgttcatgaa agtgtttttc tctttaaggt aattaaaaaa 120

cagtggaaatg	gaaaaacagt	gctgtagtca	tcttgtaata	tgctccttgt	caacaatgta	180
tacattcctg	ctaggtgcc	tattcattgc	ttaagctca	agtcgcact	tactagtga	240
gtattctgcc	aatgaaggta	agttaagact	tggtatatgc	atggagcact	tccatcta	300
cacacatctc	tctcttgcc	ttgggttctgt	tatatataac	atggaaataa	taatgccttt	360
tgcttcattgt	gagtgataaa	gcatatttaa	atttgattat	ttaaccttgc	attcctcaac	420
aagaaaaaat	gtttgataat	ggatgaaatg	tgagtcaatc	agatacaaaa	atcaaacct	480
ttggtgaaga	accagtcgta	acatttgact	gttaattcaa	tcaacagggtg	ttcttgacc	540
tatagcaaaa	tgtgtaattg	cgccttattt	tgaagtagaa	ggatataattt	gtttggtcac	600
ttggcatttg	tgaggactct	actattgtaa	ttattgtatc	aatggtaagg	tgtagcatt	660
atattgtg	gtcatattgt	atcaacagta	taaattataa	gctttgataa	gtatgtattt	720
aagaaatctt	tttttatgta	gggatttaag	caaacacttt	aattccacca	aactgtattg	780
agtacttctt	actagttatt	gagtgaaagg	gtgggttgcc	cctccacatc	tgtaggtgtt	840
tctcgtagg	tggaacgaga	gacttgga	agaaggac	atagacaaag	tatagagaaa	900
gaaaaaagg	ggcccagg	accggcgtc	agcacacgga	ggatctctgc	cagcctctga	960
gttccmttag	tatttattga	tcattattgg	gtgttctc	gagagtgga	tgtagcagga	1020
tcataggata	gtagtgaga	gagggtcaac	aggtaaacac	gtgaacaaag	gtctttgcat	1080
cataracaak	gtaaagratt	aagtgtctg	cttttagata	tgcatacaca	taaacatctc	1140
aatgctttac	aaagcagtat	tgctgcccg	akgtcccacc	tccagcccta	aggcggtttt	1200
yccctatctc	agtagatgga	gcatacaatc	gggttttata	ccgagacatt	ccattgccc	1260
gggacrggca	ggagacagat	gccttcctct	tgctcaact	gcaagaggcr	ttcttctc	1320
ttttactaat	cctcctcagc	acagaccctt	tacnggggtg	cggtctggg	gacggtcagg	1380
tctttccctt	cccacgaggc	catatttcag	actatcacat	ggggagaaac	cttgacaat	1440
acctggcttt	cctaggcaga	ggctscctgc	gcyttccrca	gtgttttg	tcctgsgta	1500
cttgagatta	gggagtggtg	atgactctta	asgagcatgc	tgcttcaag	catctgttta	1560
acaaagcaca	tcttgaccg	cccttaatcc	atttaacct	gagtkgacac	agcacatgtt	1620
tcagagagca	crgggttggg	ggtaaggtta	cagattgcag	aacaaaatgg	agtctcctat	1680
gtctacttct	ttctamacag	acacagtaac	aatctgatct	ctcttttccc	cacaattgag	1740
gacacataca	atcatgatat	gacctttaat	ggtctactac	ttggagagtc	agatgtgtac	1800
ccaagtctct	actgcagtta	acatttacct	gccaggcact	aggctaagta	ttagcagcag	1860
gttcaaagtg	cataagatat	agacctgtc	ctcaagactt	agtttattag	gagagacatg	1920
aatgtaaaca	catcatgaaa	atccattata	ataactgcaa	taattgatat	atcctgaaga	1980
tgtagagatt	gtctagagga	taaagttata	tattctgttt	ggtaggggat	gatgtggagt	2040
tcaaatggat	cagagaacac	ttcgctgatt	agaagtcagt	tgatccacta	gaagtcaagg	2100
tgaacaagg	gattcaaaac	agaggcaaca	gcctgtaaaa	gggaacagag	gcataaaaaa	2160
gcaggatatg	ttgtgagaac	atgtagtttg	aaattaccaa	gcaaaaagtt	taaggactcg	2220
tagccaggca	cagtggctca	tgctgtaatc	ccagcacttt	aggaggccaa	ggccggcgga	2280
tcacttgagg	tcaggaaattt	gagaccaggc	tgccaacat	ggtgaaaccc	atctctacta	2340
gaaatacaaa	aaattagctg	ggtttgttgg	cgtgtgcctg	taatcccagc	tatgaggag	2400
actgaagcag	gagaatgaac	ccgggaggca	gagattgcag	tgagccgaga	tcatgccact	2460
gcactccagc	ctgggcaaca	gagcaaaact	gtctcaagaa	aaaaaaaaaa	aaaaagggcg	2520
gccgc						2525

<210> 21

<211> 1396

<212> DNA

<213> Homo sapiens

<400> 21

aagtctcgta	tcgcgcccg	gaggcgccg	agcccgccg	ctggcgccg	atccaggctc	60
ctggaagaac	catgtccgg	agctactgg	catgccagg	acacactgct	gcccagagg	120
agctgctgtt	tgaattatct	gtgaatgttg	ggaagaggaa	tgccagagct	gccggtgaa	180
aattacccaa	ccaagagaaa	tctgcaggat	ggactttctg	gtcctcttct	tggtctacct	240
ggcttcgggtg	ctgatgggtc	ttgttcttat	ctgcgtctgc	tcgaaaaccc	atagcttgaa	300
aggcctggcc	aggggaggag	cacagatatt	ttcctgtata	attccagaat	gtcttcagag	360
agccrtgcat	ggattgcttc	attacctttt	ccatagcaga	aaccacacct	tcattgtcct	420
gcactgggtc	ttgcaaggga	tggtttatac	tgagtacacc	tggaagat	ttggctactg	480
tcaggagctg	gagttgtcct	tgcatcact	tctctgccc	tatctgctgc	taggtgtaa	540

10

cctgtttttt	ttcaccctga	cttgtggaac	caatcctggc	attataacaa	aagcaaatga	600
attattat	cttcatgttt	atgaatttga	tgaagtgatg	tttccaaaga	acgtgagggtg	660
ctctacttgt	gattttaagga	aaccagctcg	atccaagcac	tgcaagtgtgt	gtaactgggtg	720
tgtgcaccgt	ttcgaccatc	actgtgtttg	ggtgaacaac	tgcatcgggg	cctggaacat	780
cagggtacttc	ctcatctacg	tcttgacctt	gacggcctcg	gctgccaccg	tcgccattgt	840
gagcaccact	tttctgggtcc	acttgggtgt	gatgtcagat	ttataccagg	agacttacat	900
cgatgacctt	ggacacctcc	atgttatgga	cacggctctt	cttattcagt	acctgttctt	960
gacttttcca	cggattgtct	tcagtctggg	ctttgtcgtg	gttctgagct	tcctcctggg	1020
tggctacctg	ttgtttgtcc	tgtatctggc	ggccaccaac	cagactacta	acgagtggta	1080
cagagggtgac	tgggcctggg	gccagcgttg	tccccttgtg	gcctggcctc	cgtcagcaga	1140
gccccaaagtc	caccggaaca	ttcactccca	tgggcttcgg	agcaaccttc	aagagatctt	1200
tctacctgcc	tttccatgtc	atgagaggaa	gaaacaagaa	tgacaagtgt	atgactgcct	1260
ttgagctgta	gttcccgttt	atttacacat	gtggatcctc	gttttccaaa	aaaaaaaaaa	1320
aaaaaaaaaaaa	aaaaaaaaaaaa	aaaactcgag	ggggggcccg	gtaccaatt	cgccctggag	1380
ttcaagtaga	catcaa					1396

<210> 22
 <211> 1069
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (508)
 <223> n equals a,t,g, or c

<400> 22						
ggcacgagca	cagcctcagg	ccctgcccc	gacctgcaga	atcagaaact	ctgggggtgag	60
gcctgggttat	ctgctgtaac	agaccttcca	gtgggttctg	atgccctcta	gagcaggaga	120
accactagct	tagagggttc	agtatgtttg	gcactcttgc	atttgtgtta	gttcagaggga	180
atggctgacc	cccatgtctc	atttctaagc	ttcaggcagc	ttttctcctg	ggcagctgtc	240
attctgttga	ggggaatcct	ggggactgtg	gctcctcctc	cctgtccgtg	tgctcctgat	300
ctggcagctc	accccccttca	tctccccgtg	gagggtccat	gcctagagggt	ggtcttcaaa	360
cagaagaatg	gcaaagataa	ttgtctcgtg	ttttaccctg	acccatttcc	tttaagaggg	420
tcacttcttg	gcccattcat	taaaaaccaa	tgctatagtt	ctgtgattcc	actatcagac	480
agtgccacgt	ccaaggcgcg	ggctcttnac	ctccctggaa	gagagactgt	gctgtctgtg	540
cttccctgtgt	tctccagtc	cacgctccca	cggaccacg	cccttgagga	ctccctcggg	600
gtcccagggc	ttctgggtgtg	ttcagagacc	tccacactca	acgaccactg	gtgctgcaga	660
agggccgggtg	cttacattcc	aattaacaga	cgcttttccc	atctaagtcc	tcttgcccttc	720
tcttaacacc	acctcgggag	tgtttatgtc	tattctaagt	gaatttcact	gtgtgaaaaa	780
attcacacct	gttggtcccag	cgatttggga	ggccggggcg	ggtgtatcat	ttgagcccag	840
gagtttgagg	ctagcctggg	caggatgggtg	aaaccccgtc	tctataaaga	aatttttaaa	900
attagctggg	catagtggca	cgtgcctgta	gttccatcta	ctggggaggc	tgggggtggga	960
ggatcgcata	agcccgggag	tttgaggctg	cagtgtgctg	tgatcgagc	actgcactcc	1020
agtctgggca	acagagcaag	accctgtctc	ttaaaaaaaa	aaaaaaaaaa		1069

<210> 23
 <211> 1658
 <212> DNA
 <213> Homo sapiens

<400> 23						
ggcacgagcc	ggcctgccag	agccatgcc	ctgactcttc	agcttcaaaa	tcaggggtct	60
caggacagag	gatgctgggt	gggctcagag	ctcatcaggg	gggctgtgtg	tgagagggga	120
tgcccttctgg	atgccctcat	cctcctcggg	gctgggggtct	ccctcaaggc	caccagctc	180
cttcctttgt	ttgtgtgtgc	tactcctgcc	gctgtgtgcc	ttggccctgc	tgctcttctt	240

11

cttggacttc	ttccctccca	gggcagctgt	gtctcccttc	ttgccggacc	actgctctgc	300
caggcaacct	aggggtgtgga	ggagagagac	cctcaacaga	agtgcctcag	ggctggggtg	360
ctgggcaagg	agcactgagc	agggagccgt	gggagtagca	actgggactg	tgcttgacat	420
cagcctccct	gcctcctgce	tctcgctgtg	gccaccaggc	ccctctgggg	gcatctgact	480
tgctctgcca	tcattctgca	cctgggtttca	gtgactctta	cttcaccatg	tcttgccaat	540
caagcctttc	aagggcagag	atcctacaat	gccctctggt	gccctctggt	tctctccta	600
cccacctccc	ccaagggaga	gcaaacaaat	catccagagc	cagcctgccc	ttgcttcccc	660
aaactcactg	gtgtcttttc	ccttcagcac	gtgggtggcg	cagaggaatt	cagtcagggtc	720
ttcctcctgg	tgatcctgt	accagtcctc	gatcacctcc	tcaaactctt	caccagcaca	780
tcacacttgt	taatcataat	acctcatatt	ggcaaagccc	cagcacctga	ctcgctccta	840
gaggagctca	gcctaagcct	cgcaaccac	tgcaaggtag	cagtggcacg	gttcacctaa	900
ggaaactgag	gccagagagg	tgaaatgacc	tgaccaaagc	caccccgcc	tggtgggact	960
tcctcagagc	agaccaatc	cccaccagcc	cttcactggg	cacagcaacc	cttccaaggg	1020
ctgaagggcc	tgtacctgct	tcttgagggtc	agccacttct	gcagaagtct	cgttcaacag	1080
ctcatagggg	atgtccatca	ccaccttgac	ccctttgtgt	accagggtgt	gtaatgtctc	1140
aaaggctctc	gacatgccct	ggaagaagcg	accagatatg	gcaggcggag	ctcccttctc	1200
tcctccccc	cctcgctctc	cagtgggtggc	taagaacca	gctataagac	caatgtctca	1260
cgccctctaa	ggatcctcat	cctttttttt	ttgagaagga	gtctcactct	gtcgcccagg	1320
ttggagcgtc	tcagctcact	gcaacctctg	cctcccaggt	tcaagcgatt	ttcctgcctc	1380
agcctcccaa	gcagctggga	ctacaaaggc	gtgccaccat	acccggctaa	ttttgtaga	1440
gttgggggtt	tgcatgttg	gtcaggctgg	tctcgaaact	ctagcatcaa	gttttccact	1500
cacctcagcc	tcccaaagt	ctgagattac	aggcgtgagc	caccgcacct	ggcctcatcc	1560
ttgacctgac	cttctcttc	cctcttttag	gcctgcttcc	cacaaccct	gcacatatat	1620
cccctgatct	gcctctgcac	acctcatcgc	ttcaaaaa			1658

<210> 24

<211> 1077

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1036)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1038)

<223> n equals a,t,g, or c

<400> 24

ggcacgaggg	gaaagccatg	ctcccaggac	tccttccttg	cagccttaaa	tcggtctgta	60
cggaaaattc	cgcgccttag	aaaccacgc	ttgggtgtaa	cttattattg	ttcttcctga	120
cctacttcct	gtttatcact	tccgggttca	tcatttttggc	atttcggtga	tcgggttgga	180
actattgaag	cccgttttca	ggttcttttc	cccatttttc	ctttgaaagg	aagacttctg	240
gcttctccta	aatctccgtt	ctctgggtaa	ggggagtcca	agcctctgtc	atgaggaacg	300
gaaatgcgag	ggcctcgggt	gttactctaa	aatccgcct	cagcttgac	gccggaagct	360
gcgattcctg	cagcggaaga	ggcgtgatct	ggccttcgac	tcgctatgtc	cactaacaat	420
atgtcggacc	cacggaggcc	gaacaaagt	ctgaggtaca	agccccgcc	gagcgaatgt	480
aacccggcct	tggaagaccc	gacgccggac	tacatgaacc	tgctgggcat	gatcttcagc	540
atgtgcggcc	tcattgcttaa	gctgaagtgg	tgtgcttggg	tcgctgtcta	ctgctccttc	600
atcagctttg	ccaactctcg	gagctcggag	gacacgaagc	aaatgatgag	tagcttcatg	660
ctgtccatct	ctgccgtggt	gatgtcctat	ctgcagaatc	ctcagcccat	gacgccccca	720
tggtgatacc	agcctagaag	ggtcacattt	tggacctgt	ctatccacta	ggcctgggct	780
ttggctgcta	aacctgctgc	cttcagctgc	catcctggac	ttccctgaat	gaggccgtct	840
cggtgccccc	agctggatag	agggaaacct	gccctttcct	agggaaacac	ctaggcttac	900
ccctcctgcc	tccttccccc	tgctgtctgc	tgggggagat	gctgtccatg	tttctagggg	960

12

tattcatttg	ctttctcggt	gaaacctgtt	gttaataaag	tttttctactc	tgaaaaaaaa	1020
aaaaaaaaa	aaaaancncg	agggggggcc	cggaacccaa	ttcscgggat	agtgagt	1077

<210> 25
 <211> 1205
 <212> DNA
 <213> Homo sapiens

<400> 25						
cccacgcgtc	cgcagaggca	gggcaatagt	ggagttcttg	cttggccaag	cagcctagaa	60
ctcaaagtcc	atggcccctt	ctgggccttg	agaaattgga	tggttatagc	accaggcagc	120
ccttggtggg	gggggacagc	aaatgaggga	cctctctttt	ctctacactc	tcctttgggt	180
cccgagatc	tggcaggccc	tggctggagg	cataagatta	gatgaggttg	agctggttga	240
gaatgaagct	gtgttgggag	aagaaatgag	gttgtaccgg	aagatcaacg	aggttgtgct	300
gtcagggaat	gaggtggtac	ttgggggcaa	gtgaggctgc	attattagat	aaatgaggtt	360
gtactgtcag	gggatgaagt	gtactttag	tagagatgac	gtcctgcttg	atcagtcggc	420
ttttgctcca	tcagagaaca	cagccacacc	acaggaggaa	ggagagtgtc	cgactcagag	480
gataaatgag	gggtgcctgc	tggataaatg	agggggcccg	tcaggtgaat	ggagtgcctg	540
tagcaaatga	ggttgacttt	gctggataaa	tgggactggg	gtgctggata	aatgggggtg	600
tgctgtcagg	tgaatgcatt	actgctcgtg	ggtgaagggc	atcctgggaa	taatgagggt	660
gtcctgctgg	atagatgagc	tgccaccacc	aaatggatca	gacctgttcc	atgaaggagg	720
caccatcagc	aacgacgagg	ttatcctgtt	ccactggggg	ctcctggagc	gtcttctggc	780
ccaggggaaa	ctcgggtgtg	gccaccctgg	gttatccaag	tctctctggg	gagcagggtg	840
gggggctggg	gagggcaggc	agctgcattg	tgcaccgtgg	gacctctcct	tcacccccaa	900
tggatgccct	actcctctcc	ctggcacccc	tcagtgggtc	agactgcttc	ggacattctc	960
acccactgc	ctgcttctca	tcctgcctgt	gtcttctttc	tgcccagttt	ggaaaagccc	1020
ctattatgtg	tcagccactc	tgcccagttc	tatttaatct	ccctataaca	cagtattact	1080
cctccttgca	catacacact	ttctcttatt	cattcatcca	ttcattcatt	tgacaacacat	1140
ttaagtgtct	agtatgtacc	aaacacatga	ggtacagttt	taaaaagaat	aaaaaaaaaa	1200
aaaaa						1205

<210> 26
 <211> 1674
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1663)
 <223> n equals a,t,g, or c

<400> 26						
cccagcagc	tgagtcctt	ccctgtcttt	cactcttctg	gcatcggttg	ttttacttct	60
tcgattgaac	cctgcttct	cgacccccct	gggaggccgc	cttcttcagg	cgctccctt	120
ctctccacga	gtcgtctctg	acagctgagg	aactggcaag	atcctgctac	ccagagggtg	180
aatgggtatc	tttcccgaa	taatccta	ttttctaagg	gtgaagttg	caacggcggc	240
cgtgattgta	agcggagtaa	gcaaacacct	ccattgtatt	agtcaccaga	aaagtaccac	300
tgtaagtcat	gagatgtctg	gtctgaattg	gaaacccttt	gtatatggcg	gccttgccctc	360
tatcgtggct	gagtttggga	ctttccctgt	ggaccttacc	aaaacacgac	ttcaggttca	420
aggccaaagc	attgatgccc	gtttcaaaga	gataaaatat	agagggatgt	tcctatgcgt	480
gtttcgcatc	tgtaaagagg	aaggtgtatt	ggctctctat	tcagggaattg	ctcctgcgtt	540
gctaagacaa	gcatcatatg	gcaccattaa	aattgggatt	taccaaagct	tgaagcgctt	600
attcgtagaa	cgtttagaag	atgaaactct	tttaattaat	atgatctgtg	gggtagtgtc	660
aggagtgata	tcttccacta	tagccaatcc	caccgatgtt	ctaaagattc	gaatgcaggc	720
tcaaggaagc	ttgttccaag	ggagcatgat	tggaaagctt	atcgatatat	accaacaaga	780
aggcaccagg	ggtctgtgga	gggtgtgtgt	tccaactgct	cagcgtgctg	ccatcgttgt	840

13

aggagtagag	ctaccagtct	atgatattac	taagaagcat	ttaatatgt	caggaatgat	900
gggcgataca	attttaactc	acttcgtttc	cagctttaca	tgtggtttgg	ctggggctct	960
ggcctccaac	ccggttgatg	tgggtcgaac	tcgcatgatg	aaccagaggg	caatcgtggg	1020
acatgtggat	ctctataagg	gcactgttga	tggtatttta	aagatgtgga	aacatgaggg	1080
cttttttgca	ctctataaag	gattttggcc	aaactggcct	cggtctggac	cctggaacat	1140
catttttttt	attacatacg	agcagctaaa	gaggcttcaa	atctaagaac	tgaattatat	1200
gtgagccag	ccctgccagc	ctttctactc	ctttgccctt	ttcccgtgtt	ctaattgtatt	1260
ttgacaatgt	tgtaatgtgt	taccaagccg	ttggtctcct	aagggcctcc	tgatggaaga	1320
acagtggggg	ggttcaaagt	tatttctatg	tttgtgttac	catgttaact	tttccccgag	1380
agaaagtgtt	aacattgaga	ctctggcccc	agattgggtat	cttctatgaa	gatggatact	1440
gatgggtgac	attgaaaacg	gcctgctttc	caaatgtggt	taaatgtaat	tggttagccc	1500
cagacttggg	ctagagcaga	aggcataggg	caggggtggt	attgctatat	gtgttacaga	1560
cctcggttct	cattaaagta	tttattggca	gaatcaaaaa	aaaaaaaaaa	aaaaaaaaaa	1620
aaactcgagg	gggggcccgg	tacccaattc	gcctatggt	gantcgaatg	ggct	1674

<210> 27

<211> 1965

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (333)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1961)

<223> n equals a,t,g, or c

<400> 27

ggatcctcgc	ggcggcgggc	gtgcttacag	cctgagaaga	gcgtctcgcc	cgaggagcggc	60
ggcggccatc	gagaccacc	caaggcgct	ccccctcggc	ctcccagcgc	tcccagccg	120
cagcgccgc	gccccttcag	ctagctcgct	cgctcgctct	gcttccctgc	tgccggctgc	180
gcatggcgtt	ggcgttgccg	gcgctggcgg	cggtcgagcc	ggcctgcggc	agccgggtacc	240
agcagttgca	gaatgaagaa	gagtctggag	aacctgaaca	ggctgcagggt	gatgctcctc	300
cacctttacag	cagcatttct	gcagagagcg	cancatattt	tgactacaag	gatgagctctg	360
ggtttccaaa	gccccatct	tacaatgtag	ctacaacact	gcccagttat	gatgaagcgg	420
agaggaccac	ggctgaagct	actatccctt	tggttctctg	gagagatgag	gattttgtgg	480
gtcgggatga	ttttgatgat	gctgaccagc	tgaggatagg	aaatgatggg	attttcatgt	540
taactttttt	catggcattc	ctctttaact	ggattggggt	tttctctgtc	ttttgcctga	600
ccacttcagc	tgcaggaagg	tatggggcca	tttcaggatt	tggtctctct	ctaattaaat	660
ggatcctgat	tgtcagggtt	tccacctatt	tccttgata	ttttgatggt	cagtactggc	720
tctggtgggt	gttctctgtt	ttaggctttc	tcctgtttct	cagaggattt	atcaattatg	780
caaaagttcg	gaagatgcca	gaaactttct	caaatctccc	caggaccaga	gttctcttta	840
tttattaaag	atgttttctg	gcaaaggcct	tcctgcattt	atgaattctc	tctcaagaag	900
caagagaaca	cctgcaggaa	gtgaatcaag	atgcagaaca	cagaggaata	atcacctgct	960
ttaaaaaat	aaagtactgt	tgaagagatc	atttctctct	atttggtcct	aggtgtaaaa	1020
ttttaatagt	taatgcagaa	ttctgtaatc	attgaatcat	tagtggttaa	tgtttgaaaa	1080
agctcttgca	atcaagtctg	tgatgtatta	ataatgcctt	atatattggt	tgtagtcat	1140
ttaagtagca	tgagccatgt	ccctgtagtc	ggtagggggc	agtcttgctt	tattcatcct	1200
ccatctcaaa	atgaacttgg	aattaaatat	tgtaagatat	gtataatgct	ggccatttta	1260
aaggggtttt	ctcaaaagtt	aaacttttgt	tatgactgtg	tttttgaca	taatccatat	1320
ttgctgttca	agttaattcta	gaaatttatt	caattctgta	tgaacacctg	gaagcaaaat	1380
catagtgcaa	aaatacat	aagggtgtgt	caaaaataag	tctttaattg	gtaaataata	1440
agcattaatt	ttttatagcc	tgtattcaca	attctgcggg	accttattgt	acctaaggga	1500
ttctaaaggt	gttgtcactg	tataaaacag	aaagcactag	gatacaaatg	aagcttaatt	1560

14

actaaaatgt	aattcttgac	actcttttcta	taatttagcgt	tcttcacccc	cacccccacc	1620
ccccccccc	ttatttttct	tttgtctcct	ggtgattagg	ccaaagtctg	ggagtaagga	1680
gaggattagg	tacttaggag	caaagaaaaga	agtagcttgg	aacttttgag	atgatcccta	1740
acatactgta	ctacttgctt	ttacaatgtg	ttagcagaaa	ccagtgggtt	ataatgtaga	1800
atgatgtgct	ttctgcccac	gtggtaattc	atcttgggtt	gctatgttaa	aactgtaaat	1860
acaacagaac	attaataaat	atctcttgtg	tagcaccttt	aaaaaaaaa	aaaaaaaaa	1920
aaaaaaaaa	aaaaaaaaa	aaaaaaaaa	aaaaaaaaa	naaaa		1965

<210> 28

<211> 1863

<212> DNA

<213> Homo sapiens

<400> 28

gactaggccg	cgagcttagt	cctgggagcc	gcctccgtcg	ccgccgtcag	agccgcccta	60
tcagattatc	ttaacaagaa	aaccaactgg	aaaaaaaaat	gaaattcctt	atcttcgcat	120
ttttcgggtg	tgttcacctt	ttatccctgt	gctctgggaa	agctatatgc	aagaatggca	180
tctctaagag	gacttttgaa	gaaataaaaag	aagaaatagc	cagctgtgga	gatgttgcta	240
aagcaatcat	caacctagct	gtttatggta	aagcccagaa	cagatcctat	gagcgattgg	300
cacttctggg	tgatactggt	ggacccagac	tgatgggtc	caagaacctt	gaaaaagcca	360
tccaaattat	gtaccaaacc	ctgcagcaag	atgggtgga	gaaagttcac	ctggagccag	420
tgagaatacc	ccactgggag	aggggagaag	aatcagctgt	gatgctggag	ccaagaattc	480
ataagatagc	catcctgggt	cttggcagca	gcattgggac	tcctccagaa	ggcattacag	540
cagaagttct	ggtggtgacc	tctttcgatg	aactgcagag	aagggcctca	gaagcaagag	600
ggaagattgt	tgtttataac	caaccttaca	tcaactactc	aaggacggtg	caataccgaa	660
cgaggggggc	ggtggaagct	gccaaaggtg	gggctttggc	atctctcatt	cgatccgtgg	720
cctccttctc	catctacagt	cctcacacag	gtattcagga	ataccaggat	ggcgtgcccc	780
agattccaac	agcctgtatt	acggtggaag	atgcagaaat	gatgtcaaga	atggcttctc	840
atgggatcaa	aattgtcatt	cagctaaaga	tgggggcaaa	gacctacca	gatactgatt	900
ccttcaacac	tgtagcagag	atcactggga	gcaaatatcc	agaacagggt	gtactggtca	960
gtggacatct	ggacagctgg	gatgttgggc	aggggtccat	ggatgatggc	ggtggagcct	1020
ttatatcatg	ggaagcactc	tcacttatta	aagatcttgg	gctgcgtcca	aagaggactc	1080
tgcggtctgt	gctctggact	gcagaagaac	aagggtggagt	tgggtgccttc	cagtattatc	1140
agtacacaa	ggtaaataat	tccaactaca	gtctggtgat	ggagtctgac	gcaggaaacct	1200
tcttaccac	tgggctgcaa	ttcactggca	gtgaaaaggc	cagggccatc	atggaggagg	1260
ttatgagcct	gctgcagccc	ctcaatatca	ctcaggctct	gagccatgga	gaagggacag	1320
acatcaactt	ttggatccaa	ctcgagtgac	ctggagccag	tctacttgat	gacttataca	1380
agtatttctt	cttccatcac	tcccacggag	acaccatgac	tgtcatggat	ccaaagcaga	1440
tgaatgttgc	tgctgctgtt	tgggctgttg	tttcttatgt	tgttgacagc	atggaagaaa	1500
tgctgcctag	gtcctagaaa	cagtaagaaa	gaaacgtttt	catgcttctg	gccaggaatc	1560
ctgggtctgc	aacttttgaa	aactcctctt	cacataacaa	tttcatccaa	ttcatcttca	1620
aagcacaact	ctatttcatg	ctttctgtta	ttatctttct	tgatactttc	caaattctct	1680
gattctagaa	aaaggaatca	ttctcccctc	cctcccacca	catagaatca	acatatggta	1740
gggattacag	tgggggcatt	tctttatatc	acctcttaaa	aacattgttt	ccactttaaa	1800
agtaaacact	taataaat	ttggaagatc	tctgaaaaaa	aaaaaaaaa	aaagggcggc	1860
cgc						1863

<210> 29

<211> 1626

<212> DNA

<213> Homo sapiens

<400> 29

cccagcgtc	cggagccggg	agccgggtcg	gggggctccg	ggctgtggga	ccgctggggc	60
cccagcgatg	gcgaccctgt	ggggaggcct	tcttcggctt	ggctccttgc	tcagcctgtc	120
gtgcctggcg	ctttccgtgc	tgctgctggc	gcactgtcag	acgccgcca	gtgattgcct	180

15

tcatgttgtg	gagcccatgc	ctgtgcgggg	gcctgatgta	gaagcatact	gtctacgctg	240
tgaatgcaaa	tatgaagaaa	gaagctctgt	cacaatcaag	gttaccatta	taatttatct	300
ctccattttg	ggccttctac	ttctgtacat	ggtatatctt	actctgggtg	agcccatact	360
gaagaggcgc	ctctttggac	atgcacagtt	gatacagagt	gatgatgata	ttggggatca	420
ccagcctttt	gcaaattgcac	acgatgtgct	agcccgcctcc	cgcagtcgag	ccaacgtgct	480
gaacaaggta	gaatatgcac	agcagcgctg	gaagcttcaa	gtccaagagc	agcgaagctc	540
tgtctttgac	cggcatgttg	tcctcagcta	attgggaatt	gaattcaagg	tgactagaaa	600
gaaacaggca	gacaactgga	aagaactgac	tgggttttgc	tgggtttcat	tttaatacct	660
tgttgatttc	accaactggt	gctggaaatt	caaaactgga	agcaaaaact	tgcttgattt	720
ttttttcttg	ttaacgtaat	aatagagaca	tttttaaaag	cacacagctc	aaatcagcca	780
ataatctttt	cctattgtga	cttttactaa	taaaaataaa	tctgcctgta	aattatcttg	840
aagtccttta	cctggaacaa	gcactctctt	tttcaccaca	tagttttaac	ttgactttca	900
agataatttt	cagggttttt	gttgtgtgtg	ttttttgttt	gtttgttttg	gtgggagagg	960
ggagggatgc	ctgggaagtg	gttaacaact	tttttcaagt	cactttacta	aacaaacttt	1020
tgtaaataga	ccttaccttc	tattttcgag	tttcatttat	attttgcagt	gtagccagcc	1080
tcacaaaga	gctgacttac	tcatttgact	tttgactga	ctgtattatc	tgggtatctg	1140
ctgtgtctgc	acttcatggt	aaacgggatc	taaaatgcct	ggtggctttt	cacaaaaagc	1200
agattttctt	catgtactgt	gatgtctgat	gcaatgcata	ctagaacaaa	ctggccattt	1260
gctagtttac	tctaaagact	aaacatagtc	ttggtgtgtg	tggtcttact	catcttctag	1320
tacctttaag	gacaaatcct	aaggacttgg	acacttgcaa	taaagaaatt	ttattttaaa	1380
cccaagcctc	cctggattga	taatatatac	acatttgta	gcatttccgg	tcgtggtgag	1440
aggcagctgt	ttgagctcca	atgtgtgcag	ctttgaacta	gggctggggt	tgtgggtgcc	1500
tcttctgaaa	ggtctaacca	ttattggata	actggctttt	ttcttctctt	ttggaatgta	1560
acaataaaaa	taatttttga	aacatcaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1620
aaaaaa						1626

<210> 30

<211> 605

<212> DNA

<213> Homo sapiens

<400> 30

ccacgcgtcc	gcccacgcgt	cggggaaatg	accttggaga	ttgtagcaga	gagtgcagat	60
gaggagcggc	ctgctggcca	gggcccggat	gagcccaaca	tgaaccctaa	gcttgaggac	120
ccaaggcggc	ccgacacctc	cttcctgtgg	tttacctccc	catacaagac	catgaagttc	180
atcctgtggc	ggcgtttccg	gtgggccatc	atcctcttca	tcctcctctt	catcctgctg	240
ctgttccttg	ccatcttcat	ctacgccttc	ccgaactatg	ctgccatgaa	gctggtgaag	300
cccttcagct	gaggactctc	ctgccctgta	gaagggggccg	tgggggtccc	tccagcatgg	360
gactggcctg	cctcctccgc	ccagctcgcc	gagctcctcc	agacctccta	ggcctgattg	420
tcctgccagg	gtgggcagac	agacagatgg	accggcccac	actcccagag	ttgctaacaat	480
ggagctctga	gatcacccca	cttccatcat	ttccttctcc	cccaacccaa	cgcttttttg	540
gatcagctca	gacatatttc	agtataaaac	agttggaacc	acaaaaaaaa	aaaaaaaaaa	600
aaaaa						605

<210> 31

<211> 931

<212> DNA

<213> Homo sapiens

<400> 31

gagagtgcct	aagcgggggt	gaaagaggac	gtgttaccca	ctgccatgca	ccaggactgg	60
ctgtgttaacc	ttgggtggcc	cctgctgtct	ctctgggctg	cagagtctgc	cccacatgtg	120
gccatggcct	ctgcaactgc	tcagctcttg	tccaggccct	gtggcaggac	acacatggtg	180
agcctagccc	tgggacatca	ggagactggg	ctctggctct	gttcggcctt	tgggtgtgtg	240
gtggattctc	cctgggcctc	agtgtgcccc	tctgtaaaagg	ggcagctgac	agtttgtggc	300
atcttgccaa	gggtccctgt	gtgtgtgtat	gtgtgtgcat	gtgtgcgtgt	ctccatgtgc	360

16

gtccatattt	aacatgtaaa	aatgtccsc	crckcgctccg	cccaaacatg	ttgtacattt	420
caccatggcc	ccctcatcat	agcaataaca	ttcccactgc	caggggttct	tgagccagcc	480
aggccctgcc	agtggggaag	gaggccaagc	agtgcctgcc	tatgaaattt	caacttttcc	540
tttcatacgt	ctttattacc	caagtcttct	cccgctccatt	ccagtcaa	ctgggctcac	600
tcaccccagc	gagctctcaa	atccctctcc	aactgcctaa	ggccctttgt	gtaagggtgc	660
ttaatactgt	cctttttttt	tttttaacag	tgttttgtag	atttcagatg	actatgcaga	720
ggcctggggg	acccctggct	ctgggcccgg	cctgggggctc	cgaaattcca	aggcccagac	780
ttgcgggggg	tgggggggta	tccagaattg	gttgtaaata	ctttgcatat	tgtctgatta	840
aacacaaaca	gacctcaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	900
aaaaaaaaaa	aaaaaaaaaa	aaagggcggc	c			931

<210> 32

<211> 1407

<212> DNA

<213> Homo sapiens

<400> 32

gaattcggca	cgagggcagg	ctcagaagac	gatgcggggc	tgtgtgccgg	ccttcttctg	60
gcattgtact	agcctcagga	gagcttgctg	caccagggcc	gccaggtctt	tcacagcaca	120
actgcctgga	aggcaggttg	cgagaaggag	aggcggtatg	catgagcagc	aagggggacc	180
gatgctgtgc	agctcacacc	actccagaac	ctgacaaggc	accagcagga	ccccttgcca	240
ggagcatgtc	tgtgcagcag	tgtttttgcc	cctgcacatt	ccagaagccc	tcatgggaag	300
ggatgcagcc	aggcagactc	ctgccagatg	gggcaggtag	tttattcaaa	gagaactctg	360
tatcccatag	gccagggctc	tcctttcgct	tggcggtggc	tttgctggcc	cagtgtgtgc	420
tcctggctca	gcagaaacat	ccatttgagt	tggcatccct	gtagggatcc	cagagcgttg	480
taagccttct	tgtgatttgt	agggatggct	gtgggggtgg	ttccaggagg	ggccaccat	540
tgccgcatct	acttctagac	tcccaaagga	gccagggctc	aggcaggcct	ggccagagt	600
cacgctggga	accacgagtt	tgggaagcag	tcgtattctc	tctctctctc	tctctctctc	660
agtatccatg	acagggtatg	aacatattgt	ctctttataa	atgtcatttt	acaaattatg	720
tgattatctg	gaagctctaa	gatgagagca	aatgcctgat	cactctggcc	aaatgtcaga	780
tactaaagcc	cattcttggc	cgggcatgtt	ggctcccggc	kgtaatccca	gcactttggg	840
aagcccaagt	gggtgaatca	cctgaggtca	ggagttcaag	accagcctga	ccaacatggg	900
gataccccgt	ctctactaaa	aatacaagcc	ggcggtggtg	gcgcatgcct	gtaatcccag	960
ctactcagga	ggctgaggca	ggaaaatcac	ttgaactcgg	gaggcagagg	ttgcagttag	1020
ctgagatcgc	gccattgcac	tccagcctgg	gtgacagagc	aagactctgt	ctcataaata	1080
aatacaaaag	ccattcttcc	agagtcttgt	gccttaaata	aaacacacct	ctctgctgtg	1140
ggaagactgt	gcaatggcac	agccgcagag	cttggttttg	gaggttgaag	tgctctgggg	1200
agaattcgta	gatcatcctc	agaaaagcct	tgccctgggt	ttctaccaga	aaaacgtctc	1260
ccaatcacc	aggaaagctg	tccacagtag	tccccctta	tccacggtgt	cactttccat	1320
gggttcagtt	atctgcggtc	aaccacggtc	tgacaatatt	aaatggaaaa	ttcttcaaac	1380
agttaaaaaa	aaaaaaaaaa	aactcga				1407

<210> 33

<211> 1526

<212> DNA

<213> Homo sapiens

<400> 33

ggcacgagaa	aaaaccttca	ggcgcccat	gggtatgccc	aagaggacag	agaacgaatg	60
cacagaaata	ttgtcagcct	tgcacagaat	ctcctgaact	ttatgattgg	ctctatcttg	120
gattttatgg	aatgcttcc	ctggttttac	attggttctt	cattgaatgg	tactcgggga	180
aaaagagtcc	cagcgcaatt	ttccaacaca	tcactgcatt	atttgaatgc	agcatggcag	240
ctattatcac	cttacttgtg	agtgatccag	ttggtgttct	ttatattcgt	tcagtctcag	300
tattgatgct	ttctgactgg	tacacgatgc	tttacaaccc	aagtccagat	tacgttacca	360
cagtacactg	tactcatgaa	gccgtctacc	cactatatac	cattgtattt	atctattacg	420
cattctgctt	ggtattaatg	atgctgctcc	gacctcttct	ggtgaagaag	attgcatgtg	480

17

ggttagggaa	atctgatcga	tttaaaagta	tttatgctgc	actttacttc	ttcccaattt	540
taaccgtgct	tcaggcagtt	ggtggaggcc	ttttatatta	cgccttccca	tacattatat	600
tagtggtatc	tttggttact	ctggctgtgt	acatgtctgc	ttctgaaata	gagaactgct	660
atgatcttct	ggtcagaaag	aaaagactta	ttgttctctt	cagccactgg	ttacttcatg	720
cctatggaat	aatctccatt	tccagagtgg	ataaacttga	gcaagatttg	ccccctttgg	780
ctttggtacc	tacaccagcc	cttttttact	tgttcactgc	aaaatttacc	gaaccttcaa	840
ggatactctc	agaaggagcc	aatggacact	gagtgtagac	atgtgaaatg	ccaaaaacct	900
gagaagtgct	cctaataaaa	aagtaaatca	atcttaacag	tgtatgagaa	ctattctatc	960
atatatggga	acaagattgt	cagtatatct	taatgtttgg	gtttgtcttt	gttttgttta	1020
tggttagact	tacagacttg	gaaaatgcaa	aactctgtaa	tactctgtta	cacagggtaa	1080
tattatctgc	tacactggaa	ggccgctagg	aagcccttgc	ttctctcaac	agttcagctg	1140
ttcttttaggg	caaaatcatg	tttctgtgta	cctagcaatg	tgttcccatg	ttattaagaa	1200
aagctttaac	acgtgtaatc	tgcagtcctt	aacagtggcg	taattgtacg	tacctgttgt	1260
gtttcagttt	gtttttcacc	tataatgaat	tgtaaaaaca	aacatacttg	tggggtctga	1320
tagcaaacat	agaaatgatg	tattattgtt	tttgttatct	atttattttc	atcaatacag	1380
tattttgatg	tattgcaaaa	atagataata	atttatataa	cagggtttct	gtttatagat	1440
tggttcaaga	tttgtttgga	ttattgttcc	tgtaaagaaa	acaataataa	aaagcttacc	1500
tacataaaaa	aaaaaaaaaa	aaaaaa				1526

<210> 34

<211> 1737

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1674)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1731)

<223> n equals a,t,g, or c

<400> 34

gtcgacccc	gcgtccgccc	acgcgtccgc	ccacgcgtcc	ggtttataaa	cagaagttaa	60
aaacttgtaag	cttaagcttc	cgtttataaa	cagaagttaa	aaattatagg	tcctgttttaa	120
cattcagctc	tgtaactca	ctcatctttt	tgtgttttta	cactttgtca	agatttcttt	180
acataattcat	caatgtctga	agaagttact	tatgcagatc	ttcaattcca	gaactccagt	240
gagatggaaa	aaatcccaga	aattggcaaa	tttggggaaa	aagcacctcc	agctccctct	300
catgtatggc	gtccagcagc	cttgtttctg	actcttctgt	gccttctgtt	gctcattgga	360
ttgggagtct	tggcaagcat	gtttcatgta	actttgaaga	tagaaatgaa	aaaaatgaac	420
aaactacaaa	acatcagtga	agagctccag	agaaatattt	ctctacaact	gatgagtaac	480
atgaatatct	ccaacaagat	caggaacctc	tccaccacac	tgcaaacaaat	agccacaaa	540
ttatgtcgtg	agctatatag	caaagaacaa	gagcacaaat	gtaagccttg	tccaaggaga	600
tggatttggc	ataaggacag	ctgttatttc	ctaagtgatg	atgtccaaac	atggcaggag	660
agtaaaatgg	cctgtgctgc	tcagaatgcc	agcctgttga	agataaacia	caaaaatgca	720
ttggaattta	taaaatccca	gagtagatca	tatgactatt	ggctgggatt	atctcctgaa	780
gaagattcca	ctcgtggtat	gagagtggat	aatataatca	actcctctgc	ctgggttata	840
agaaacgcac	ctgacttaaa	taacatgtat	tgtggatata	taaatagact	atatgttcaa	900
tattatcact	gcacttataa	acaaaagaatg	atatgtgaga	agatggccaa	tccagtgcag	960
cttgggtctc	catatttttag	ggaggcatga	ggcatcaatc	aaatacattg	aaggagtgtg	1020
kgggggtggg	gttctaggct	ataggtaaat	ttaaatat	ttctggttgac	aattagttga	1080
gtttgtctga	agacctggga	ttttatcatg	cagatgaaac	atccaggtag	caagcttcag	1140
agagaataga	ctgtgaatgt	taatgccaga	gaggtataat	gaagcatgtc	ccacctccca	1200
ctttccatca	tggcctgaac	cctggaggaa	gaggaagtcc	attcagatag	tgtggggggc	1260
cttcgaattt	tcattttcat	ttacgttctt	ccccttctgg	ccaagatttg	ccagaggcaa	1320

18

catcaaaaac	cagcaaattt	taattttgtc	ccacagcggt	gctaggggtg	catggctccc	1380
catctcgggt	ccatcctata	cttccatggg	actccctatg	gctgaaggcc	ttatgagtca	1440
aaggacttat	agccaattga	ttgttctagg	ccaggttaaga	atggatatgg	acatgcattt	1500
attacctctt	aaaattatta	ttttaagtaa	aagccaataa	acaaaaacga	aaaggcaagt	1560
tacgagactg	acttattttt	aacttctgtg	tggttagcta	ctgtaagctt	ggcttttgtt	1620
aaagacatac	agcaattagc	tatgcaaaca	taagcattgt	tctgaaaaaa	aatntataga	1680
tagatatgtt	tatctcccat	aactcataac	tggggagtat	tatacccccg	nggctttt	1737

<210> 35

<211> 2242

<212> DNA

<213> Homo sapiens

<400> 35

tgcacccacg	cgcccggtg	gccatggcgg	cgccggcgcc	gctcccgagc	tcctggggccc	60
tcttctcgcc	gctcctcgca	gggcttgca	tactgggagt	cgggccgggc	ccagcgcggg	120
cgctgcacaa	cgtcacggcc	gagctctttg	gggcccaggc	ctggggcacc	cttgccggtt	180
tcggggacct	caactccgac	aagcagacgg	atctcttcgt	gctgcccggaa	agaaatgact	240
taatcgtctt	tttggcagac	cagaatgcac	cctattttta	acccaaagta	aaggatatctt	300
tcaagaatca	cagtgcattg	ataacaagt	tagtccctgg	ggattatgat	ggagattctc	360
aaatgggatg	ccttctgaca	tatcttccca	aaaattatgc	caagagtga	ttaggagctg	420
ttatcttctg	gggacaaaat	caaacattag	atcctaaca	tatgaccata	ctcaatagga	480
cttttcaaga	tgagccacta	attatggatt	tcaatggtga	tctaattcct	gatatttttg	540
gtatcacaaa	tgaatccaac	cagccacaga	tactattagg	agggaaattta	tcattggcatc	600
cagcattgac	cactacaagt	aaaatgcgaa	ttccacattc	tcattgcattt	attgatctga	660
ctgaagattt	tacagcagat	ttattcctga	cgacattgaa	tgccaccact	agtaccttcc	720
agtttgaat	atgggaaaat	ttggatggaa	acttytstgw	magtacymta	ttggaaaaac	780
ctcaaaatat	gatggtgggt	ggacagtcag	catttgccaga	ctttgatgga	gatggacaca	840
tggtacattt	actgccaggc	tgtgaagata	aaaattgcca	aaagagtacc	atctacttag	900
tgagatctgg	gatgaagcag	tggtgtccag	tcctacaaga	tttcagcaat	aagggcacac	960
tctggggctt	tgtgccattt	gtggatgaac	agcaaccaac	tgaaatacca	attccaatta	1020
cccttcatat	tgagacttac	aatatggatg	gctatccaga	cgctctgggc	atactaaaga	1080
acacatctgg	aagcaaccag	caggcctttt	tactggagaa	cgctccctgt	aataatgcaa	1140
gctgtgaaga	ggcgcgtcga	atgttttaag	tctactggga	gctgacagac	ctaaatcaaa	1200
ttaaggatgc	catggttgcc	accttctttg	acatttacga	agatggaatc	ttggacattg	1260
tagtgctaag	ttaaggatat	acaaagaatg	attttgccat	tcatacacta	aaaaataact	1320
ttgaagcaga	tgcttatttt	gttaaagtta	ttgttcttag	tggtctgtgt	tctaattgact	1380
gtcctcgtaa	gataacaccc	tttggagtga	atcaacctgg	accttatatc	atgtatacaa	1440
ctgtagatgc	aaatgggtat	ctgaaaaatg	gatcagctgg	ccaactcagc	caatccgcac	1500
atttagctct	ccaactacca	tacaacgtgc	ttggttttag	tcggagcgca	aattttcttg	1560
accatctcta	cgttgggtatt	ccccgtccat	ctggagaaaa	atctatacga	aaacaagagt	1620
ggactgcaat	cattccaaat	tcccagctaa	ttgtcattcc	ataccctcac	aatgtccctc	1680
gaagttggag	tgccaaactg	tatcttacac	caagtaatat	tggtctgctt	actgctatag	1740
ctctcatcgg	tgtctgtgtt	ttcatcttgg	caataattgg	cattttacat	tggcaggaaa	1800
agaaagcaga	tgatagagaa	aaacgacaag	aagcccaccg	gtttcatttt	gatgctatgt	1860
gacttgccct	taatattaca	taatggaatg	gctgttcact	tgattagtgt	aaacacaaat	1920
tctggcttga	aaaaataggg	gagattaaat	attattttata	aatgatgtat	cccatggtaa	1980
ttattggaaa	gtattcaaat	aaatatgggt	tgaatatgtc	acaaggctct	tttttttaaa	2040
gcactttgta	tataaaaatt	tggttctctt	attctgtagt	gctgtacatt	tttgttcctt	2100
tgtggaatgt	gttgcatgta	ctccagtgtt	tgtgtattta	taatcttatt	tgcatcatga	2160
tgatggaaaa	agttgtgtta	ataaaaaata	ttaaatgagc	aggaaaaaaa	aaaaaaaaaa	2220
aaaaaaaaaa	aaggcgggcc	gc				2242

<210> 36

<211> 2235

<212> DNA

<213> Homo sapiens

<400> 36

gtaattcggc	acgaggggttc	caccaacatg	gagctctcgc	agatgtcgsa	gctcatgggg	60
ctgtcgggtg	tgcttgggct	gctggccctg	atggcgacgg	cgggcggtasc	gcgggggtgg	120
ctgcgcgcg	gggaggagag	gagcgccgg	ccgcctgcc	aaaaagcaaa	tggatttcca	180
cctgacaaat	cttcgggac	caagaagcag	aaacaatatc	agcggattcg	gaaggagaag	240
cctcaacaac	acaacttcac	ccaccgcctc	ctggctgcag	ctctgaagag	ccacagcggg	300
aacatatctt	gcatggactt	tagcagcaat	ggcaaatacc	tggtctacctg	tgcagatgat	360
cgcaccatcc	gcatctggag	caccaaggac	ttcttgcagc	gagagcaccg	cagcatgaga	420
gccaacgtgg	agctggacca	cgccaccctg	gtgcgcttca	gccctgactg	cagagccttc	480
atcgtctggc	tggccaacgg	ggacaccctc	cgtgtcttca	agatgaccaa	gcgggaggat	540
gggggctaca	ccttcacagc	cacccagag	gacttcccta	aaaagcacia	ggcgccgtgc	600
atcgacattg	gcattgctaa	cacaggaag	tttatcatga	ctgcctccag	tgacaccact	660
gtcctcatct	ggagcctgaa	gggtcaagtg	ctgtctacca	tcaacaccaa	ccagatgaac	720
aaacacacag	ctgctgtatc	tccttgtggc	agatttgtag	cctcgtgtgg	cttcacccca	780
gatgtgaagg	tttgggaagt	ctgctttgga	agaaggggg	agttccagga	ggtgggtgca	840
gccttcgaac	taaagggcc	ctccgcggt	gtgactcgt	ttgctttctc	caacgactca	900
cggaggatgg	cttctgtctc	caaggatggt	acatggaaac	tgtgggacac	aratgtggaa	960
tacaagaaga	agcaggaccc	ctacttgcgt	aagacaggcc	gctttgaaga	ggcgccgggt	1020
gccgmccgt	gcccgcctgg	cctctccccc	aagccccagg	tcttggcctt	ggccagtggc	1080
agtagtattc	atctctacaa	tacccggcgg	ggcgagaagg	aggagtgtct	tgagcggttc	1140
catggcgagt	gtatcgccaa	cttgtccttt	gacatcactg	gccgctttct	ggcctcctgt	1200
ggggaccggg	cggtgcggct	gtttcacaac	actcctggcc	accgagccat	ggtggaggag	1260
atgcagggcc	acctgaagcg	ggcctccaac	gagagcacc	gccagaggct	gcagcagcag	1320
ctgaccagg	cccaagagac	cctgaagagc	ctgggtgccc	tgaagaagtg	actctgggag	1380
ggcccgggcg	agaggattga	ggaggaggga	tctggccctc	tcatggcact	gctgccatct	1440
ttcctcccag	gtggaagcct	ttcagaagga	gtctcctggt	tttyttactg	gtggccctgc	1500
ttcttcccat	tgaactact	cttgtctact	taggtctctc	tcttcttgct	ggctgtgact	1560
cctccctgac	tagtgcccaa	ggtgcttttc	ttcctcccag	gccagtgagg	tggaatctgt	1620
ccccacctgg	cactgaggag	aatggtagag	aggagaggag	agagagagag	aatgtgattt	1680
ttggccttgt	ggcagcacat	cctcacaccc	aaagaagttt	gtaaatgttc	cagaacaacc	1740
tagagaacac	ctgagtacta	agcagcagtt	ttgcaaggat	gggagactgg	gatagcttcc	1800
catcacagaa	ctgtgttcca	tcaaaaagac	actaagggat	ttccttcttg	gcctcagttc	1860
tatttgtaag	atggagaata	atcctctctg	tgaactcctt	gcaaagatga	tatgaggcta	1920
agagaatatc	aagtcgccag	gtctggaaga	aaagtagaaa	agagtagtac	tattgtccaa	1980
tgatcatgaa	gtggtaaaag	tgggaaccag	tgtgctttga	aaccaaatta	gaaacacatt	2040
ccttgggaag	gcaaagtgtt	ctgggacttg	atcatacatt	ttatatggtt	gggacttctc	2100
tcttcgggag	atgatattct	gtttaaggag	acctcttttc	agttcatcaa	gttcatcaga	2160
tatttgagtg	cccactctgt	gccccaaata	atatgagctg	gggattaaaa	aaaaaaaaaa	2220
aaaaaaaaaa	ctcga					2235

<210> 37

<211> 2971

<212> DNA

<213> Homo sapiens

<400> 37

gacgtgagga	gcgttccatt	tggccagtgg	tgggcggttg	ccacagctgg	tttagggccc	60
cgaccactgg	ggccccctgt	caggaggaga	cagcctcccg	gccccggggag	gacaagtgcg	120
tgccaccttt	ggctgccgac	gtgattccct	gggacgggtc	gtttcctgcc	gtcagctgcc	180
ggccgagttg	ggtctccgtg	gttcaggccg	gctccccctt	cctgggtctc	cttctccgcg	240
ttggccgggt	tatcgggagg	agattgtctt	ccagggctag	caattggact	tttgatgatg	300
tttgaccacg	cggcaggaat	agcaggcaac	gtgatttcaa	agctgggctc	agcctctggt	360
tcttctctcg	tgtaatcgca	aaacccattt	tggagcagga	attccaatca	tgtctgtgat	420
ggtggtgaga	aagaaggtga	cacggaaatg	ggagaaactc	ccaggcagga	acaccttttg	480
ctgtgatggc	cgcgtcatga	tggcccgga	aaagggcatt	ttctacctga	cccttttctt	540

catcctgggg	acatgtacac	tcttcttcgc	ctttgagtgc	cgctacctgg	ctgttcagct	600
gtctctgcc	atccctgtat	ttgctgccat	gctcttcctt	ttctccatgg	ctacactggt	660
gaggaccagc	ttcagtgacc	ctggagtgat	tcctcgggcg	ctaccagatg	aagcagcttt	720
catagaaatg	gagatagaag	ctaccaatgg	tgcggtgccc	cagggccagc	gaccaccgcc	780
tcgtatcaag	aatttccaga	taaacaacca	gatttgtaaa	ctgaaatact	gttacacatg	840
caagatcttc	cggcctcccc	gggcctccca	ttgcagcatc	tgtgacaact	gtgtggagcg	900
cttcgaccat	cactgccctt	gggtggggaa	ttgtgttgga	aagaggaact	accgctactt	960
ctacctcttc	atcctttctc	tctccctcct	cacaatctat	gtcttcgcct	tcaacatcgt	1020
ctatgtggcc	ctcaaactct	tgaaaattgg	cttcttggag	acattgaaag	aaactcctgg	1080
aactgttcta	gaagtcctca	tttgcttctt	tacactctgg	tccgtcgtgg	gactgactgg	1140
atctcatact	ttcctcgtgg	ctctcaacca	gacaaccaat	gaagacatca	aaggatcatg	1200
gacagggaag	aatcgcgctc	agaatcccta	cagccatggc	aatattgtga	agaactgctg	1260
tgaagtgtcg	tgtggcccct	tgccccccag	tgtgctggat	cgaaggggta	ttttgccact	1320
ggaggaaagt	ggaagtcgac	ctcccagtac	tcaagagacc	agtagcagcc	tcttgccaca	1380
gagcccagcc	cccacagaac	acctgaactc	aaatgagatg	ccggaggaca	gcagcactcc	1440
cgaagagatg	ccacctccag	agcccccaga	gccaccacag	gaggcagctg	aagctgagaa	1500
gtagcctatc	tatggaagag	acttttggtt	gtgtttaatt	agggctatga	gagatttcag	1560
gtgagaagtt	aaacctgaga	cagagagcaa	gtaagctgtc	ccttttaact	gtttttcttt	1620
ggctcttagt	caccagttg	cacactggca	ttttcttgct	gcaagctttt	ttaaatttct	1680
gaactcaagg	cagtggcaga	agatgtcagt	cacctctgat	aactggaaaa	atgggtctct	1740
tgggccctgg	cactgggtct	ccatggcctc	agccacaggg	tccccttgga	ccccctctct	1800
tccctccaga	tcccagccct	cctgcttggg	gtcactggtc	tcattctggg	gctaaaagtt	1860
tttgagactg	gtcaaatcc	tcccaagctg	ctgcacgtgc	tgagtcacga	ggcagtcaca	1920
gagacctctg	gccaggggat	cctaactggg	ttcttggggg	cttcaggact	gaagaggagg	1980
gagagtgggg	tcagaagatt	ctcctggcca	ccaagtgcc	gcattgccca	caaatccttt	2040
taggaatggg	acaggtacct	tccacttggt	gtatttatta	gtgtagcttc	tcctttgtct	2100
cccatccact	ctgacaccta	agccccactc	ttttccatt	agatatatgt	aagtagttgt	2160
agtagagata	ataattgaca	tttctcgtag	actaccaga	aactttttta	atacctgtgc	2220
cattctcaat	aagaatttat	gagatgccag	cggcatagcc	cttcacactc	tctgtctcat	2280
ctctcctcct	ttctcattag	ccccttttaa	ttgtttttc	cttttgactc	ctgctcccat	2340
taggagcagg	aatggcagta	ataaaagtct	gcactttggt	catttctttt	cctcagagga	2400
agcctgagtg	ctcacttaaa	cactatcccc	tcagactccc	tgtgtgaggg	ctgcagaggc	2460
cctgaatgca	caaatgggaa	accaaggcac	agagaggctc	tcctctcctc	tcctctcccc	2520
cgatgtaccc	tcaaaaaaaa	aaaaaatgct	aaccagttct	tccattaagc	ctcggttgag	2580
tgagggaaag	cccagcactg	ctgcctcttc	gggtaactca	ccctaaggcc	tcggcccacc	2640
tctggctatg	gtaaccacac	tgggggcttc	ctccaagccc	cgctcttcca	gcacttccac	2700
cggcagagtc	ccagagccac	ttcacccctg	gggtgggctg	tggeccccag	tcagctctgc	2760
tcaggacctg	ctctatttca	gggaagaaga	tttatgtatt	atatgtggct	atatttctta	2820
gagcacctgt	gttttctctc	ttctaagcca	gggtcctgtc	tggatgactt	atgcggtggg	2880
ggagtgtaaa	ccggaacttt	tcattctatt	gaaggcgatt	aaactgtgtc	taatgcaaaa	2940
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	a			2971

<210> 38

<211> 1163

<212> DNA

<213> Homo sapiens

<400> 38

ccacgcgtcc	gccaaaggtg	ctgattaggg	aatggttatg	gactaggagt	atcagtaaca	60
atggttagaa	agtggctaac	atthgttgag	cacctgctgt	gtgcctggcc	ccggctggga	120
gccttcgtgc	ccagagtgc	cccgtctgaa	tgagttcttt	tgctcattc	aaactgggga	180
gtgggaggca	gagctgcaca	actcacaggt	gccgagctca	agactcactc	ctgggtctgc	240
ctgggctggg	ctgtgcttgt	tgccccctgt	gccaacacac	gcgcaccttt	cacctgaaag	300
ccaggatccg	cagaacgttc	cccaggagg	tcattgtttg	gcactatgat	ttgtctcttc	360
ctaaaaaggt	gatagagtta	cactggagag	agcagcatcc	aggtgcagca	gggatggggc	420
tggggctcac	gggcaggggc	tctgtgtccg	gctggggcct	ggggtcctgc	gctgcacctg	480
tgtgtcagaa	gcactcagta	aatctttgct	gatgaaggat	gacaggatat	aggacatgat	540

21

gcttgcgtgct	gcattgcctg	caatcctgga	tgaatgccca	ggttggcctt	gctccccgtc	600
gggtggatgt	gacgttagct	gtgatgttag	gtccctggct	ttaaaatacg	acggaactgg	660
gaattgaggg	agcagttggg	gcagaaagga	cagccccgca	gaggcctgga	gctgagcagt	720
gcggggcgacc	caggagcagt	gagtgetttcc	gtcacagcct	tcatacgacc	ctgtggtcct	780
cataaagggg	atggaatcta	cgaatttagt	tttcccagcc	tccttaaaaa	ctcattcatg	840
ccagggggcag	tggctcacac	ctgaaatccc	accactttgg	gaggctgagg	caggctgatt	900
acttgaggctc	aggagtttga	gaccagccta	gccaacatgg	tgaacccccg	tgtctactca	960
aagtacaaaa	aaaaaaatta	gtcagacgtg	gtgtcacgca	cctgtaatcc	cagctctttg	1020
ggaggtgag	gcaggagaat	cacttgaacc	caggaggcag	aggttatagt	gagccagtat	1080
tgccgcactg	acctccatct	gggcaataga	gtgagaccct	gtctcaaaaa	aaaaaaaaaa	1140
aaaaaaaaaa	aaaaaaaaaa	aaa				1163

<210> 39

<211> 1932

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1624)

<223> n equals a,t,g, or c

<400> 39

ggcacgagcc	aggccccctgg	gccgggcgct	gaggcgggcc	cctctgggca	gggccccggc	60
ggggctgggt	gggccgcccc	tgctgctgcc	gtccatgctg	atgtttgcgg	tgatcgtggc	120
ctccagcggg	ctgctgctca	tgatcgagcg	gggcatcctg	gccgaratga	agccccctgcc	180
cctgcacccg	cccggcccg	arggcacagc	ctggcgcggg	aaagccccc	agcctggggg	240
cctgtccctc	agggtcgggg	acgcggactt	gcaagtgcgg	caggacgtcc	ggaacaggac	300
cctgcggggc	gtgtgcggac	agccaggcat	gccccgggac	ccctgggact	tgccggtggg	360
gcagcggcgc	accctgctgc	gccamatcct	cgtaagtgc	cgttaccgct	tcctctactg	420
ctacgtcccc	aaggtggcct	gctctaactg	gaagcgggtg	atgaaggtgc	tggcaggcgt	480
cctggacagc	gtggacgtcc	gcctcaagat	ggaccaccgc	agtacactgg	tgctcctggc	540
cgacctgcgg	cctgaggaga	ttcgctaccg	cctgcagcac	tactttaagt	tcctgtttgt	600
gcgggagccc	ttggaacgcc	tcctctctgc	ctaccgcaac	aagtttggcg	agatccgaga	660
gtaccagcaa	cgctatgggg	ctgagatagt	gaggcggtac	agggctggag	cggggcccag	720
ccctgcaggc	gacgatgtca	cattccccga	gttcctgaga	tacctggtgg	atgaggaccc	780
ctatgacttt	gtgggtcctc	atgagaggct	ggaggctgat	gcaaatcagg	tgctggagtg	840
ggtacgggca	ccacctcacg	tccgatttcc	agctcgccag	gcctggtacc	ggccagccag	900
ccccgaaagc	ctgcattacc	acttgtgcag	tgcccccccg	gccctgctgc	aggatgtgct	960
gcctaagtat	atcctggayt	tytccctctt	tgccatacca	ctgcctaata	tcaccaagga	1020
ggcgtgtcag	cagtgcacat	gggtgtgggg	ccagcagctg	gtggggactg	gtttcaacgc	1080
cagctttctg	tgcttctgcc	tgctattcgg	agaaactctg	gctctggggc	ttggggcttc	1140
tcaggatcct	ggatggcaga	gactgccctc	agaarttcct	tgtccagggt	gggcaccac	1200
agtgcactag	aggacagggc	taggcaggag	acctgctgct	cctcattggg	gggatctctt	1260
ggggggcaga	caccagtttg	ccaatgaagc	aacacatctg	atctaaagac	tggtccaga	1320
ccccgggctg	ccaggattat	gcagtccact	tggtctacct	taatttaacc	tggtggccaaa	1380
ctcagagatg	gtaccagcca	ggggcaagca	tgaccagagc	cagggaccct	gtggctctga	1440
tccccatctt	atccacccca	tgtgcctcag	gactagagtg	agcaatcata	ccttataaat	1500
gacttttgtg	cctttctgct	ccagtctcaa	aatttcctac	acctgccagt	tctttacatt	1560
tttnccaagg	aaaggaaaac	ggaagcaggg	ttcttgctcg	gtagctccag	gacctcctc	1620
tgcaggcacc	caaagaccct	ctgtgccag	cctcttctct	gagttctcgg	aacctcctcc	1680
ctaattctcc	cttctctccc	cacaaggcmt	ttgaggttgt	gactgtggct	ggtatatctg	1740
gctgccattt	ttctgatgca	tttattttaa	atttgtactt	tttgatagaa	cccttgtaag	1800
ggctttgttt	tcctaataagc	tgacttttta	ataaagcagt	tttatataaa	aaaaaaaaaa	1860
aaaaaaaaaa	aa					1920
						1932

<210> 40
 <211> 881
 <212> DNA
 <213> Homo sapiens

<400> 40
 gaattcggca cgagggaacc cagaagatgc tgcctctcct gatcatctgt ctcctgcctg 60
 ccattgaagg gaagaactgc ctccgctgct ggccagaact gtctgccttg atagactatg 120
 acctgcagat cctctgggtg accccagggc caccacaga actttctcaa agtattcact 180
 ccttgttcct agaggataat aattttctca aaccctggta ccttgatcgt gaccatttgg 240
 aagaagaaac agccaaattc ttcaactcaag tacaccaagc cattaataacg ttacgagatg 300
 ataaaacagt acttctggaa gagatctaca cgcacaagaa tctctttact gagaggctga 360
 ataagatatc tgatgggctg aaggagaagg gagccccacc cytctccatg aatgccttcc 420
 cggctccatc tcctacttgc accccagaac cccttggctc tgtctgcctc ccagcacct 480
 cagtttctct accttctcac ctccctggca gcctgcaatg agtcctgtgc caggaaccgg 540
 cggacctccc tgtgggctgt gagtctcagc agtgccttac tcctggccat agctggagat 600
 gtttctttta ctggcaaagg aagaaggagg cagtaaagga acagggcagc ccgcatgtct 660
 tccagaagtg aacagaggcc gcagctacca ccgtcacaaa gttcactcat ctctgggtcc 720
 cgggtgacccc atccccccat accctccatc ctgggtcctg gggcccaaaa gctctgaggc 780
 ctaggagact gcgctgtctc gtggtttgcc tactcctaca cctttgtaaa gagtctcttc 840
 attaaaaccc ctcttcataa aaaaaaaaaa aaaaaactcg a 881

<210> 41
 <211> 1932
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (2)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1022)
 <223> n equals a,t,g, or c

<400> 41
 cncggcgcg ctcggctcat gccccggggc gcggggcaca caggccggcc ggcagccgct 60
 gggaaatagg cccccggggg cgggtggcggc ggcggggcca tggcgcgag accccgggcg 120
 ccggccgcct ccggggagga gttctccttc gtcagcccg cgggtgaaata cctgctcttc 180
 ttcttcaaca tgcctctctg ggtgatttcc atggtgatgg tggctgtggg tgtctacgct 240
 cggctaatag agcatgcaga agcagcccta gcctgcctgg cagtggacct tgccatcctg 300
 ctgatcgtgg tgggtgtcct catgttctct ctcaccttct gtggctgcat tgggtccctc 360
 cgcgagaaca tctgcctcct gcagacgttc tcctctgccc tcaccgctgt gttcctgctg 420
 cagctggccg ctgggatacct gggcttcgct ttctcagaca aggctcgagg gaaagtgagt 480
 gagatcatca acaatgccat tgtgcactac cgagatgact tggatctgca gaacctcatt 540
 gattttggcc agaaaaagtt tagctgtgtg ggagggattt cctacaagga ctggtctcag 600
 aacatgtatt tcaactgctc agaagacaac ccagtcgag agcgtgctc tgtgccttac 660
 tcctgttgct tgcctactcc tgaccaggca gtgatcaaca ctatgtgtgg ccaaggatg 720
 caggcctttg actacttgga agctagcaaa gtcacttaca ccaatggctg tattgacaag 780
 ttggtcaact ggatacacag caacctatc ttacttgggt gtgtggctct aggcctggcc 840
 atccccagc tgggtgggaat tctgctgtcc cagatcctag tgaatcagat caaagatcag 900
 atcaagctac agctctacaa ccagcagcac cgggtgacc catggtactg agaatccatc 960
 ctgcacctcc tcaccatgga aactggcaag cctcataaac gaacagcagt gggtgctgaa 1020
 ancagcacca aatggagatt tggattccag cccccagtg acagccagtg ggaagaagc 1080

23

aaactccaga	tgggcagaag	gcagggtgca	caggtggctc	cagtctcagg	aggatgcgcc	1140
tcctctcccc	catcccagcc	ctcagcattg	tgccagagt	atacccttaa	gtgtttgggt	1200
ttatgttttc	agttttgttt	gggaaacagc	agttgcacag	agagttgggg	gtactgctgc	1260
tgcccttttca	ccgaggcact	gccaccacca	gctctascag	ggatgctcct	gagcttggcg	1320
gacatactta	gacctaacg	tgccagttag	acctggctgt	ggagagtagc	actggcagcc	1380
ctgcctggac	tccacttggc	atgataccag	ctccagaagg	gaagggagtg	gagcaggcag	1440
tgaggagaga	gcctgggggt	cggctgggga	cagccgtatg	tgctaggtag	gagtggaggg	1500
agatatgttt	accaaagcc	tgtcctgcca	tcctcccagg	tagtcagagt	gagctacatc	1560
ctgccccgcc	ttcatttcca	tggaaacatg	gcagctagga	cacgggggtac	aacagcagcc	1620
aaattcttcc	ccacctccct	tacttcgaaa	aaaagtgttg	aaccttggtc	cctatactct	1680
gcagtcagaa	gtgggactga	gccatacatg	cccttgaatt	cctccctgtc	tgccctccc	1740
tctccagcaa	gcagggtttt	ctttaacttg	gcagtgtgca	gaggagaagt	ggtaacaccc	1800
ccaccccatt	cccctgcacg	ggagctcagt	attcctacag	ggtaagaggt	aggaatcttg	1860
ctgggacgag	gggagccaga	agtggcaata	aaagcgtgtt	gacctggaaa	aaaaaaaaaa	1920
aagggcggcc	gc					1932

<210> 42

<211> 1164

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (582)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (592)

<223> n equals a,t,g, or c

<400> 42

ggcacgagct	tgtgtgtcac	cagcctcctg	atctgccagg	gtctgtcttg	ggttggcact	60
gaccagggtg	tcacgtcctt	gctgcccgtg	cctcggctgg	aaggcatccc	caagatcaca	120
gggaaaggca	tggtctcact	caatgggcac	tgtgggcctg	tgcccttcct	ggctgtggct	180
accagcatcc	tgccccctga	catcctgcgg	agtgaaccagg	aggaggctga	ggggccccgg	240
gctgaggagg	acaagccaga	cgggcaggca	cacgagccca	tgcccgacag	ccacgtgggc	300
cgagagctga	cccgaagaa	gggcacctc	ttgcagtacc	gcctgcgctc	caccgcacac	360
ctccccggcc	cgctgtcttc	catgcgggag	ccggcgcctg	ctgatggcgc	agctttggag	420
cacagcgagg	aggacggctc	catttacgag	atggccgacg	accccgacgt	ctgggtgcgc	480
agccggccct	gcgcccgcga	cgcccaccgc	aaggagattt	gctctgtggc	catcatctcg	540
gcgggcaggg	ctaccgcaac	tttggcagcg	ctctgggcac	antgggaagc	angccccgtg	600
tggggagacg	gacagcacc	tcctcatctg	gcagtggcct	tgatgctata	gcgcctcccc	660
tctcccctca	gagggcacag	ctgcaggcct	gaccaaggcc	acgcccggct	ctcgtgtctt	720
aggacctgca	cgggacttgt	ggatgggcct	ggactctcca	gaaactactt	gggccagagc	780
aaaggaaaa	ctcttgtttt	aaaaaaattt	ttttcagagt	gttttgggga	ggagttttag	840
ggcttgggga	gagggaggac	acatctggag	gaaatggcct	tctttttaaa	agcaaaaaac	900
acaaaaacct	acaactgcct	ggcaagccca	gtatcacttg	tttggggcct	agcgggactc	960
caaggcagcc	acacgcccct	cctggaaggg	tgtgtgcgtg	tgagtgtgtg	cgagtgtgtg	1020
ggctgtgtgt	tgaatatcta	ttaaataagta	tatatgggtg	atattatatg	tgtataaata	1080
aagtctgtac	atattggagc	tctgggagat	gctggaataa	aagacaagag	ttacatcttg	1140
acttggaaaa	aaaaaaaaaa	aaaa				1164

<210> 43

<211> 1105

<212> DNA

<213> Homo sapiens

<400> 43

gaattcggca cgagaacaaa ttgaaacccat-ctgggtcatga-actttttat	60
tttctaatat tgattcaatc tctttgctta ttctaaatgt gttcagattt tccacttctt	120
gagtcatttt ggtaatttat ttgtttctag gaatttgtcc atttcatcta gtttacctaa	180
tttttgacat ataaaattat atatggaaat ttctaaaata tttaaaaatt tctgtaatgt	240
caatagtaat gtcccctctt ttgtttacaa ttgtttat	300
tcaatctagc taaaaatttg tcaattttgt tctgtctctc aaaaaaatat acgtttgtct	360
tcatgatttc tctawtgttt ttccatcyat atttcatttg aatacatttt taaacyttay	420
ctttattatt tcattccttc tgggagcttt ggggtctcatt ttttttctct gataatctag	480
ttgtttattg tataagatta agtatttatt tgaaatctgt atgttcttta atgtaggcat	540
tcactactat aaatttactt ctcaggagca tctctgccgc attccatggt ttagtatgtt	600
gtgttttaat ttgtattcat aactagaggg aaacagagggt gacggagaaa aagacgtaca	660
aatatcatcc acttgcaaag tatagatttg ttgtattgk ratatgaatr aaaatattac	720
gagacagata agaaaaatttg aacactgacc attgatgcag ttacagttta ttttaaaatc	780
aagggttaata acatttttagt tatttttaaag aatgatagta atttagagat gtattctgaa	840
tgttttttaa tgaaaagata tgcctgggat ttcttccaaa atgaatcttg taggttggga	900
agaaaatgag aacatagtggt aaacaagact gacaatgagt tgttgagggt gggcaatgag	960
tacactaaag cttatttttat cttattttac tgtatatact gttaaagctt gcattatttt	1020
cataaatgca tttgctaagt gcaactgtta tcaataaaag tggattgggc tctaaaaaaa	1080
aaaaaaaaaa aaactcgagg gggggg	1105

<210> 44

<211> 1262

<212> DNA

<213> Homo sapiens

<400> 44

cagcatgtac ccagttgttc tttctcctga gaaagcaaaa tgctgatata ttcttataat	60
ccaggctgcc acgtttacct tgtaaaatca atacttaatt ttttagatttt tatattatct	120
tttctcgtga agcaagactt ctaaattatg gctataatat cttttgaatt gttgttctta	180
atgaatcttc caactgtaaa ctcacttaatt ttcaaacctta tcatacctga ggatgtaaca	240
ttgtcctttg tttctcactt tgatattacc gtcaatcatt ttgtatttct gagtacattt	300
gaacttgctg gagtaataga gggaaaacct ctgcctgatt ctaaactcaga tctttgtcct	360
atactcggac aattatgggt tcataattta ttatttttta ttttctgggt ttaacaaatg	420
agataacatt ttagacataa tatttgtaaa catcttgact tatttcagca ttttctttt	480
ttgtgtatct tcagagagtt tgttgaaagt agcaatttcc aagtaatttt aaattattga	540
agtctactag cacgaaaggt caaattctta ggatatttaa aaaatgttgt ttaataatca	600
aactcatctt aaaaaatggt catcagactc tgcctttgat gcacattttg ccaaaagaga	660
gccttatttc tgtgaaagaa atacagtatg tactttggga tttactaaag taaaactgtt	720
actttaaggg acagagcaga tatagaatcc ccctctctcc ccaactcctag tgactgggat	780
tctacattaa tatttatctt ccatgcatag tgtacttgag ggaaaaaac aataactctt	840
aattgtttta tatcaaaaca taaaatcctg tgtatcagtg actgtcaata gatggcttct	900
tgttttaaaa ctgaagctac tccagaagta ggaattaatt tatttagtaa acaaagtcag	960
tcaaacacaga gccatgtcct ggggaactgt caaagaatg gttcctaagg gccagaggcc	1020
acatccactg gtagatgaca gaacaacct acttcagatg gcaaaaccgg tcagtttggt	1080
ttgcgttggt tgcttatcct ctttctgtgt gcttcagctg aattaagtgc ttggagagct	1140
caaatagttc aagatagcca agatgaccaa ttctgccagg tggcaagcct gatcttgcaa	1200
ttttgattaa aataaagaac attccccaag aacagtttgt tgcaaaaaaa aaaaaaaaaa	1260
aa	1262

<210> 45

<211> 517

<212> DNA

<213> Homo sapiens

<400> 45
gaattcggca cgagtgcact tccaccagct atgtatgaga cttcccattg ctccacatct 60
ccagtatttt atgtgggtcag tcccttttgtt tttgggtcatt ttgggtggata tgaaatggca 120
tctcagtgtg gctttttcatt atatttcctt gatgactaat ggtattcttt caccctttca 180
gtgcttattg gccattcatg tatctttgtt ttttgtgtag cacttcaggt cttttgcccc 240
tagatttagt gggttgattg ctctttatta atgatttgta gggatgttat atatatcttg 300
gacacaagat tattgttaga gatacgtact tcagatattt tctcccagtc tgtagcttgc 360
ctaattatta ttattattat tatttgagat gaagtctcac tctgtcgccc aggcagaggt 420
tgcagtgggc cgagatagca ccactacact caagcctggc tgacagagtg agactctgtc 480
tcaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aactcga 517

<210> 46
<211> 858
<212> DNA
<213> Homo sapiens

<400> 46
agaaaaaatc ctacatggat attggtagga aagagagaaa ggaagtggcc agtgtcccgt 60
ggcctcttcc accttctgga ttgttgaagc tggggcctgg aggggatggc cctgccactc 120
agcagggggc actaatggga ccaagctaac ctgtccagtg agaatcctgc agggagacct 180
gagggtagca ggaagtgc ggggaaggcc cgggaaatgg agagagctgg tctggagggg 240
aggagcaagc cgcgtggggc aggccatgtg ccttttgcct gggggagtat tactcatttg 300
gagctgtgcg tctggaacgc ctgcctcaca cacaaaggac tggggcagat gtaagtctc 360
tgcagcaacg aagcgcacag ctgagagtaa cttagaaaagc acccagctaa tgctggcatc 420
ccagatcgac cccctcctcg ctgaatgttg gcatctctgt gcctcagttt cctcatctgt 480
aaatgggggt gataagaaat gtgtacacac ctcccgggca gtggggagga ttaaactgtg 540
ctctgacacg atccgggcat gttcagggtg gtatctgcag taaaccgcgc tcggaaaaatg 600
gcggcgcatc agggccagcg gtgggagctc tccgtgcttg gcttgacgcc attgtggagg 660
tggaggaggg gctgcaagac tctgagcagg aagacccgc aaagcaggaa agcagagcca 720
gagttggggg ccagccgcag aaacgagagc ccccgtagt ttgaggcacc ctttgagag 780
ggcaggaagc aggaagggtg aattttctcc aaaaccctaa aggcagagtg accccacatg 840
ataactgagt ttctcgag 858

<210> 47
<211> 6107
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (5749)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (5892)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (5896)
<223> n equals a,t,g, or c

<220>
<221> SITE

<222> (5906)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (5957)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (5966)

<223> n equals a,t,g, or c

<400> 47

gcagttagtt	ccttgatgtc	agtagtgggc	taaaggcagc	ttactgtgtg	tttgctggag	60
ctttcactca	gccaagtgtt	agagtcagga	aaccattga	ggcaatggcg	tcaaatgggtg	120
tttcacaaga	atgagccatt	cagtctttgc	tcactatata	tttaatat	tattattgtt	180
gttattgtta	ttattaattg	gctttctgta	ttctatgcct	tttatttata	aagacactaa	240
gaaaacccat	gtttgtaatt	ttaataacat	ttttcccatc	ttgtaatatc	cagagctact	300
ttataaattc	tctgaaccaa	aagtattttc	ctcagtgtat	ctcttctccc	ccagccccta	360
ttgggaaaaa	ttaccagta	tagttcaggt	tatgaggagg	atcagccaca	caatccagtg	420
cttcagtttg	aaaatgtaaa	attctaacc	taaagtaggg	ttggttgaaa	tttcagacaa	480
agcaaaccca	gcaggtataa	aaagtagtat	aaatacaaat	ctgtaagtta	tttttgaatt	540
ttctgaactt	ttttctaaga	gattacatag	gagactaaag	aaatctatct	gttcaagttc	600
taattaggat	gattgttaat	actgcactgt	ggatgaagtg	gcgactggct	tgtgtgctga	660
cttctgtggt	ttagcaagag	gtttattgtt	atcaaatgct	aattggcaat	gccaagtccac	720
tgggaccaat	tttctgtttt	ataatatcta	agtttagaac	agaatatata	cctgaactgt	780
agtggtttga	tcggatggag	acagaaaacc	cgatttttat	tctcataaat	tttgtggtta	840
tttatacaag	ggctgtgcta	tgctaccata	ttcttgttca	ataataatag	gtttgttgtt	900
ttttttacat	tgtaaatgt	tccttacc	taaaggctca	tgtaagtac	aacattctga	960
aaatacaatt	tggctacgaa	gagtattcat	cttctttgaa	gctcagtggt	tgatatttgt	1020
gctaataatg	caatttctg	attcctgtta	caagtatatg	ctacatatgg	gagagactca	1080
gtgagccagc	aaaggccata	gaaacaacaa	tttattaaat	gtatttatgg	cagaaggacc	1140
taataaaact	gtgagccacc	ttttcttctt	tatattgtta	catttaagtg	ttcttgcttt	1200
cagcaactca	cattaatgct	tggagcttat	ctcttctctt	ctctctctct	ctctctctct	1260
ctgtgtgtgt	gtgtgtatgt	gtgtgtgtgt	gtgtgtgtgt	ttccttattg	tcattccatt	1320
atatatccac	accaacatgg	gtgacgataa	ttcaaatgca	tattttgcct	ctaagcttga	1380
tcattgttacc	tttatgatta	aagtatcatg	ttatttagcc	aatgcaaatc	tgttttaaaa	1440
caaatagttt	aaaaaaagaa	caagttttta	agggctttat	tatagaagaa	gtattaatga	1500
aggactttcc	ttcctccctc	ccttccctcc	cctccctgcc	tccctctctc	ccttccatct	1560
cccctccctc	cctgccttct	ttgtttctcc	ttcccttatt	cctccctccc	tcctttctcc	1620
cttccctcct	ttcttccatt	catccttcc	tgccttttat	ttttattttt	tgtaatatca	1680
catgtgctgt	agtttggaat	tttattctag	tgcatttctt	gtcctcaga	acctcagcta	1740
atctacctag	gaaaaatagt	atcaaaggaa	atgagaaagt	tgatctgag	tccctccaga	1800
actaagataa	ttctttttga	ccatttaagc	ctttataaat	gcgttttgac	catttaagcc	1860
tttataaatg	cttgtttttag	gaaagtgaat	ctgttagatg	catcaacaaa	taatgaccag	1920
gacaaaacga	tttaataatt	aaagtctcaa	atcaccatgg	ttatacattt	tcaccagaaa	1980
tagtaatctt	acaatttttc	atttttctga	tgaagatttc	tggtccaata	tctgtttcct	2040
aatagatttt	ttaaattaat	tagctttcct	ctgctttatg	accacagggt	ttatccctaa	2100
ccgagacagc	tgtcttatat	ctgcatgcct	tagactgtgt	ggagggactc	catgaagaaa	2160
gaccataggt	tagaaaaata	actcatagta	tataccctag	taagtgggtt	agtagaatct	2220
cataacatgt	attaaaaaga	ggttttcttc	tctgctgtgt	tgtgtcacta	gagcaaaatt	2280
gtagagataa	tgctcataat	gcagtaaaata	tcagaataat	ctacaatatc	atttgtggat	2340
gggtcccaggt	cccagtgctc	tagttacttt	acttcttttt	ttttttttga	gatggagtct	2400
tgtctgtctc	ctcaggetag	agcagtgtgc	gatctcagct	cactgcagcc	tccacctccc	2460
aggttcaagc	gattctcctg	cctcagcctc	ccaagtagcc	aggattacag	gcacctcca	2520
ctaggccccg	ctaatttttt	ttgtattttt	ttagtagaga	tgggggtttg	ccatgttggc	2580
caggctggtt	tcgaactcct	aacctccagt	gatccacctg	cctcggcgtc	ccaaagtgtc	2640

aggattacag	gcatgagcca	ccacatccgg	cctaattact	tctttaatcc	ccattttattt	2700
ttatgccatt	ctagcctcat	ttattaataa	aattatgttt	ttactttctc	tttcaggaaa	2760
ttttttaaat	taatatattta	tatctagatc	taatgctatg	gaaaagtgcc	tttttatcat	2820
ttataatttc	atttttcact	atttccaaaa	acacataaac	aaatagtttc	agtaggtccc	2880
agctttttact	ttttccattt	aaaccttctt	ttctccattt	cttccctttg	gcttaagaat	2940
aaaagaaaaag	gtacattgct	agaattgttt	ctttgggaga	gggtaaaaga	ttacagaatt	3000
agactgttca	gcctttatat	aaactaaatt	tgtcttcac	tcaaccagct	aatggtaggt	3060
cttatctgaa	tactcatgag	aattttagca	tctgtgaaac	tccatgcacc	agatgtgtgt	3120
aaatttcagg	aagaaaagtgt	tgaaagcatt	ttctctgatg	ttaattagat	ggaaaataat	3180
cactaaaaaca	tagtttaggt	aaagcctgat	tatgccactt	ttttttaact	agacagggca	3240
aagttgttta	tgtagtgta	cttcttgtct	atcctcagtt	aatttaccta	gacaaaaagt	3300
gtcaaaggaa	atgagaaaaa	ggttatatct	gactccctcc	agacctaaaga	taattccttt	3360
tgatcagata	cagtcagatg	gagtgccctg	gtttttgtta	attttgctc	tattccagct	3420
ccttaccaca	gcggtggtgc	ttaaagaaag	gatcatcagc	aacaggtcag	gatagttcta	3480
cctttgggat	agggtgctt	tccccgtgct	agtatttctg	tgactgttag	tggcactgag	3540
gactgcaaac	ttttatgcaa	tattcttaat	accctattga	tattatgcac	tttaatcatt	3600
ccaaagaagc	caagaatgct	gtatagtgat	gattccttcc	taatgaattc	atcttaacta	3660
tttagaatgt	tatgtccctt	ttcttttgga	tagccaactt	ggtataaatg	ttatatggat	3720
ttttctaaaa	tgactatata	ggacttaaga	ctttgaaatg	taatttactt	ataaggggaa	3780
ataattatgc	tttagcacat	catttttagaa	acgtcacatt	ttagaaacat	tcagcttgct	3840
aacctacatg	tttggaatt	cattaaaacc	agttgtctat	atattttgtg	ccatgtatat	3900
aagaacatta	caatatatct	ttttctacat	atgtagtatg	tgcaaccagt	ggttctcaga	3960
gtatggttct	cagcccacca	gctagtatca	gtatcacctg	ggaactagtt	agaaatgtaa	4020
attctttggc	cccattccag	acatactgag	tcagaaattc	tggaataggg	cccccgcaat	4080
ctgttttcac	aagccctcca	ggtgattctg	atgcacactt	taaagtttag	gaaccactgg	4140
gctaagactc	tgtagagata	tagagttttt	cttccactca	gactgatata	gttatacatt	4200
gttcttcctg	taaattcagc	ttaacctggg	tatctataat	cttttatttg	caaaagttaa	4260
ttctcagtag	tgacctataga	gatacagtag	attttatgta	catacacaaat	tagtctaatt	4320
cttgataaatt	cagtttaattt	agtttgcat	tttctacca	cttactaaaa	ggtttacatt	4380
aatgactga	tttaaatata	taggtgcaat	gttctatgtt	tattttaatt	gttatgacat	4440
ttaagtagct	aatataattg	accggtgcta	aagtctcctg	tttatccata	aaatgggtac	4500
attatgggca	gtgtaataca	agctttcttt	tcattgccta	gtactttacc	agcagaccac	4560
agttttggcc	tggttagacc	aacctcaga	acaaaatcat	cattccttgt	atttatattt	4620
gtatctgaga	tagtaaacaa	gatggctggc	caggtcaaca	tggtcacctta	acttattttt	4680
ttaataggta	aaacttcttc	aaaagtagct	tgctttgtat	aagaactaag	ctatcagtat	4740
agatatagct	atccttgagg	cttatgtttc	agacaagaat	tatttactaa	aataaataat	4800
aaacaagata	atgcattata	caatttgggc	atttctcgtt	tctcaagtgt	atgcatcatg	4860
gtaaatataa	actaaccaca	agataggtag	attgattcat	ttcattttaa	tctccttggt	4920
taattcagta	cctccataat	tgttctaatc	ttcttccac	tgtttacaaa	ttaccagtta	4980
attaactcgt	gaaagaaaaa	ttcacatata	agaataaaaa	taaatgtata	ctcactttat	5040
aaaaatcacc	actgctgtct	ttccttaata	ctagcagtg	aaatgtaagt	ggcttactct	5100
acaaattttg	tggttgcaa	atacataggc	aaactgttgg	gagctgctct	agttacattc	5160
ctcccttctt	atccctttt	tctcttcttc	actttattgc	ataacatatt	cctgtaccca	5220
aagcattcta	ccacagttct	atttgactcc	cacttgtaat	aactccttta	aaaaattcca	5280
tgtttaacca	tatgacctg	cttgcttact	catattctcc	ctccctctcc	ccttcttttc	5340
tctctcttcc	agaagtcatt	tgcttggttt	gaaatatttt	gtagggattg	cttattatat	5400
tatttttagct	gatgaacctc	aggacaacgt	ctacacacac	acacatacat	acacgcacac	5460
aaaatctcag	ctgttgaaaga	gtgggcttgg	aatcagactt	ctgtgtccag	taaaaaactc	5520
ctgcactgaa	gtcattgtga	cttgagtagt	tacagactga	ttccagtga	cttgatctaa	5580
tttcttttga	tctaataaat	gtgtctgctt	accttggttc	cttttaattg	ataagctcca	5640
agtagttgct	aattttttga	caactttaaa	tgagtttcat	tcacttcttt	tacttaagt	5700
tttaagtata	gtaccaataa	tttcattaac	ctgttctcaa	gtggtttanc	taccattctg	5760
ccatttttaa	tttttattta	attttatttg	cttgagcaca	ctgatcaacc	actgaactgc	5820
cttcttccat	tgctctgcaa	tgatataagg	gttacatttt	tgtgtatatg	gctttcatag	5880
ttgggatttc	anagcnctga	taccanatat	tttcagtttg	ttctctgggg	gaatttcatt	5940
tgcatctatg	tttttancta	tctgtntaaa	cttggttaaat	attaaaaaga	tattttgctt	6000
ctattggaac	atttgtatac	tcgcaactat	atttctgtaa	acagctgcag	tcaaaaaataa	6060
aacactgaaa	gttttcaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaa		6107

<210> 48

<211> 703

<212> DNA

<213> Homo sapiens

<400> 48

ccacgcgtcc	gcaggacatc	gttttctaca	tggtggctgt	gttcctgacc	ttcctcatgc	60
tcttccgtgg	cagggtcacc	ctggcatggg	ctctgggtta	cctgggcttg	tatgtgttct	120
atgtggcac	tgtgattctc	tgcaacctga	tctaccaacg	gcaacggaga	ggatctctgt	180
tctgccccat	gccagttact	ccagagatcc	tctcagactc	cgaggaggac	cgggtatctt	240
ctaataccaa	cagctatgac	tacgggtgatg	agtaccggcc	gctgttcttc	taccaggaga	300
ccacggctca	gatcctggtc	cgggccctca	atccccctga	ttacatgaag	tggagaagga	360
aatcagcata	ctggaaagcc	ctcaaggtgt	tcaagctgcc	tgtggagtgc	ctgctgctcc	420
tcacagtcct	cgtcgtggac	ccggacaagg	atgaccagaa	ctggaaacgg	cccctcaact	480
gtctgcatct	ggttatcagc	cccctgggtg	tggtcctgac	cctgcagtcg	gggacctatg	540
gtgtctatga	gataggcggc	ctcgttcccg	tctgggtcgt	ggtgggtgatc	gcaggcacag	600
ccttggtctc	agtgcacttt	tttgccacat	ctgacagcca	gccccccagg	cttcactggc	660
tctttgtctt	cctgggcttt	ctgaccagcg	ccctgtggat	caa		703

<210> 49

<211> 639

<212> DNA

<213> Homo sapiens

<400> 49

ggcacgagca	ttcacagggt	acaaatgctg	ctgccaaactg	tcctggccaa	atgactctgc	60
atcacaaacc	tttccttgca	tgtggagggg	atggatttac	tcagtccaac	tttgatggct	120
gcataccttc	tgccctatgt	gttctggaag	ctttaaagaa	ttatatattag	tgccctatct	180
cttattctct	acatgtgtat	tggtgtttta	ttttcacaat	tttctgttat	tgattatctt	240
gttttctatt	ttgctaagaa	aaattactgg	aaaattgttc	ttcacttatt	atcatttttc	300
atgtggagta	taaaatcaat	tttgaatttt	tgatagttac	aacccatgct	agaatggaaa	360
ttcctcacac	cttgacacct	ccctactttt	ctgaattgct	atgactactc	cttggtggag	420
gaaaagtggg	acttaaaaaa	taacaaacga	ctctctcaaa	aaaattacat	taaatcacia	480
taacagtttg	tatgccaaaa	acttgattat	ccttatgaaa	atttcaattc	tgaataaaga	540
ataatcacat	tatcaaagcc	ccaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	600
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa			639

<210> 50

<211> 867

<212> DNA

<213> Homo sapiens

<400> 50

ggcacgagca	ggtactgggt	gactgcctgg	ctgaggaaaa	gttaactaga	cacttgggga	60
aaggagatcc	aaggagagta	gaggcaaaat	gcctttgcat	gcttttcttc	ctatctcttt	120
ttctttctct	ccttctcact	ctctcccttc	cttcccttct	tcctttctct	ttcttttttt	180
tttctctttt	ccccacctc	tctgcctgcc	tccttccttc	cctcccctcc	cctcccctcc	240
ccctcccctc	ctcccctcct	tccttccttc	cttccctcct	tccttccttc	cttcccctcc	300
tcctctctcc	ctccttcctc	gccttctttc	cttcgtcttg	ccaacttgcc	agaaggagcc	360
caagaaaaag	caccagatg	cttcagtcaa	cttcttagaa	ttcttctttt	ttttatgttc	420
agaaaagatg	gaaattcatt	tctgctaaag	agaaagaaaa	aattggaaga	caggggtgaag	480
gtgaacaggc	ccattataag	aaagaaacaa	aaatctatat	tctgtctaca	aggaagcgag	540
agagagaaag	agagagaaga	aagaagtctc	aggattctaa	tgtaccaaag	ggatctcctt	600
tttcttgttt	tggtctgaaa	atttcaccaa	aagagcacag	gagaacatct	tggctaattc	660

29

attggcgatg atgtaagaaa actgagagaa atgaaagaaa tgaagaatta ctgctgcaga	720
taatatacag ccttgaggaa agaaaggctt ttaagattat agatataaag gctattgctg	780
tattctggga-taaaagaaag tctgatgtca gggaaagggg aagttggaaa aactggaaaa	840
agaaaaaaga aaaaaaaaaa aaaaaaa	867

<210> 51
 <211> 1569
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (341)
 <223> n equals a,t,g, or c

<400> 51	
gtattggcca ggctggcttc aaactcctga cctcgtgatc caccacacctt ggctcccaa	60
agtgcagaga ttacagggcat gagccactgc acctggcctc aagaaaaatt atatatcacg	120
tgggaatagga tagtagtctc tgcaactgatt ttcgttgata atggctgttc ttcttatcac	180
catttttgcta tttctttgtc tgggctatta cagggttatt acagaaattt ccagaaagac	240
ccctgcctgt cgaatgttta cttcaagctt gagctcctgg tatattatga ggaaattata	300
tgatacccca ggagaggtct tcctttccca tgccattgta naattcctaa agtaaaatta	360
atttgccttc ttgtcaaaga aggagccaat gttgttttaa aatttttagct tgagagatag	420
gtgggggaaga aattaaatag acaagtaatc mctattcaga agagaaggga gagtcatgtg	480
acgaggccca agataacttg ccaaaaatat cgcagagaaa aactagtctt tggggtccta	540
ttttttgagt ggaacatttg agttatttaa aattagaatt ttattttggg cagattagaa	600
tttctagggt atgtcatatg tgtttttaa ttgaaagctc ttaaaactcc tattgtagtt	660
taatgtcatt atccattaat ttacataaat ctgatttggg tctctatttt catcgtagac	720
tgtgtagggg caatttttcc taaagggtct gtgacatagt gctacctttt ttttaaaacc	780
tgtcttgccc aggcattatt gagtgcccc tggtgccagc atgtgtattt cagcactgta	840
tcaacaaatc atgatcatct tctctggcca ttgtgccctt tcagattcca aacttggtac	900
ctctcagtc ttcctacaaa cttagaaagt ctaatatctt aatgtttact tatgtagcaa	960
cctcccttcc tcccacccct aaatcctctt gtaattaatt attttccttt ggaacttttt	1020
aaatctacaa tttccttata atatggtaac caatattaat tttcttggtc tgcgccaagt	1080
ttgatattat acaaattggt tccagtttgg gtcagtagca caaaaccagg tattttttaa	1140
aatctatata acccttcaat gaggcagtat taattttatt aactcattaa ttcaaccaat	1200
aattcttgat tgtttactgt gttagatatt ggggtatccc caatacctga cagctgtgag	1260
caaaacaaat gccctacaca catgaggtgt acagtccagt agaaaagata aacaataagc	1320
aaattaatag ataatatgat gtccaataag gacttcaaag gaaaataaag cagagtaaag	1380
agccagagaa tgacagttag ctgtttttca catgagtcac cagaaaaggc ctctttaaag	1440
aattgacatt tgaacagaaa aacgaatcaa gggcgtaac tgtttattgc ttttattgct	1500
taccatttga ccaagcaatt ctacacatag gattcacctt aaaaaaaaaa aaaaaaaaaa	1560
aaactcgag	1569

<210> 52
 <211> 1196
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (590)
 <223> n equals a,t,g, or c

<400> 52	
gattgggtct gtttatgtga tagattactt ttattgattt gtatgttgaa ccagccttgc	60

atcctagggg	tgaagccgac	ttgggtgtgg	tgataagct	ttttgatgtg	ctgctggggt	120
tggcttgcca	gtgttttatt	agggattttt	gcgtcaatat	tcacagggga	tattggcctg	180
gaatttttct	tttttggtat	gtgtctgcca	ggtttttgga	tcaggggtgat	gctggcctca	240
taaaaataagt	tagggagggc	tccctctttt	tcttccattt	ggaagaattt	cagaaggaat	300
ggtaccagat	ccyctttgta	cctctggtag	aatttggtcg	tgaatccatc	tggctckgag	360
cttttttttt	gttggttaggc	tattaattac	tgctcaatt	tcagaacttg	ttattgggtct	420
attcagggat	ttgacttctt	cctggtttag	tcttgggagg	ttgtatgtgt	gcaggaattt	480
attcatttct	tctagatttt	ctcgtttatt	tgtgtagagg	gttttatagc	atytctctgat	540
ggtagtttgt	attctgtggg	atcagtggtg	atctccctt	tatcattttt	attgtgtcta	600
tttgattctt	ctctcttktc	ttctttatta	ttctygctaa	tggctctatg	attttggtta	660
tctyttacaa	aaacaggctt	ctagattcat	ggatgttttg	aaaggtytt	cgtgtctcta	720
tctccttcag	ttcttccctg	atcttagcta	tttcttgtct	tctgctagct	tttgaaattg	780
tttgcttttg	cttctctagt	tcttttaacc	gtgatgtcca	gtgtgtcaat	ttcagatctt	840
tccagccttc	tgatatgggc	atttaatgct	ataaatttcc	ctcttaacac	tgcttttagct	900
gtgtcctaga	gattctggta	cggtgtctct	ttgttctcat	tggtttcaaa	taacttcatt	960
atttctgcct	taattttgtt	atttaccag	cagtcattca	agagcaggtt	gttcaatttc	1020
catgtagtgt	tgtgtgtttg	agtgaatttc	ttaatcttga	gttctaattt	gattgcactg	1080
tggtctgaga	gacggttaca	atttccattc	ttttgcattt	gctgagaagt	gttttacttc	1140
caattgtgtc	tcgtgccgaa	ttcgatatca	agcttatcga	taccgtcgac	ctcgag	1196

<210> 53

<211> 945

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (295)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (875)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (914)

<223> n equals a,t,g, or c

<400> 53

gaatggtgaa	atattaagtg	ctttctcccc	caggttcagg	attatgacag	ctatgtccat	60
tcacctcttc	tgtacagcat	tgtcctgtgg	aagttctggc	cagtgcataa	aggcaattaa	120
aagaaataaa	atatcaaacg	attggaaaaga	tgtaaatgtg	tcacatttca	tagaaaacat	180
gattcataga	tatacataca	cgaatgcttt	gaattcataa	gtagattcag	ccagttgctg	240
gatataaagt	caatatacaa	aaactatttt	tatagacatg	aaacacgcaa	tgagnaaaaa	300
aattttaacca	tttttagtag	catcaaaaaa	cccccatacc	taggaatatg	aatttgtagt	360
actatttggg	atatgttgat	ggatatttat	catttccagt	ttgggattat	tataaagaaa	420
atagccctga	acatttgtaa	tatatgactt	ttgggtgaatg	tagcattcat	ttctgttgat	480
tacaaactca	ggggtgaaat	tgttgagtcc	taaggagagct	atagatgtat	tcaacttcag	540
ctgatatggc	taaaataaatt	tgcgaaaaaag	attgcatcaa	gttatgctcc	catcagcaat	600
atgagagtgc	ctgtttttcc	acattgtcag	caacactttg	tactgttact	ccttttaatt	660
ttagccgatt	tggttgaagg	tgtggtaata	tctcattgta	gtggccaggc	gtgggtctca	720
cgcctgtaat	cccagcactg	tggaagcca	aggtgggccc	atcacgaggt	caggagatcc	780
agaccatcct	ggctaacatg	atgaaaccct	gttgccctgta	gtcccaacta	cttggggaggc	840
tgaggcagga	gaatggcatg	aactcgggag	gcgngccttg	cagtgagcct	ccagcctggg	900
caacagagtg	agantctctc	aaaaaaaaaa	aaaaaaaaac	tcgag		945

<210> 54
<211> 488
<212> DNA
<213> Homo sapiens

<400> 54
ggcacgagga gagtagaggc tattcatgta atgtctataa aaaaataaca ccaaggtcgg 60
gattacaggc atgagccact gcacctggcc agtttgctta ttttgtttg tgccctctcc 120
catgggagac ctcaaggagg tatgcctgcc ccacagatgc cctggaagga cagcttgctg 180
ctcctactca gaaccacacc tgcagacaga ggaggacaga cggacactca tttgctgagc 240
acccatgtaa catgaactaa gagctgggtg gagacaatga acggtggagc catcgttccc 300
gatgtggagg gagaacagct caagaccacg gaacagcctg ctctcccgct tcctggcttc 360
cgtgcgcttt tgtccaatca ggctttttga ccaatcgcc aggcgcgcta tgtaaatctc 420
tgacattttc aaagctgtct ttttaataaa cctttcagt taaaaataaa aaaaaaaaaa 480
aaaaaaaaa 488

<210> 55
<211> 2860
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (753)
<223> n equals a,t,g, or c

<400> 55
ggcacacagg gctggcaggc ccgcggtggc tgggtgtgag gcatgaacaa attgtaccgg 60
gtatccccc cccactctg accaccagtt cctccttgga tatcactccc cctgacagggc 120
agccaccca ggctggatt tgtccctgtc tccccctttt gcttttcccc catgactaat 180
gggcaccagg tcttgcctg cctgcttctc acctctgcag tggcagcagg cccctggccc 240
cagggtgcag ccggtcagtg ggggtggatg tgccttctc caggcctgcc ctctgtccaa 300
gcccggagtg ggcttgggtg gctccctggg ggcctccagt ggggtgccagg tgggtgcccgg 360
ggttattgag ggggtggtgt atcactgtag ggacaggcct cttgccccag cctggagagc 420
tgttttcttc aggaagggtc tggagatgga gacttgtttg cgaattcacc acaactccag 480
gctgggaggg tgggtctctg ctctcagagc cgagacacca gggaggatag ccaggctgcc 540
ctgcctggga attctgctgg gccgtcaa tcaaccgcga ccaacgtggg caggaggcca 600
cagtgctcctg ccaggagcag aggggtgaag gtctgcagga ggaagaccct atcctggtgg 660
ggggcacctg ctgcccaccc tgccccagc gtgctgggg ggagcacacc tgggcatgga 720
ggagtccagg gtgctgggg acacaagaga gnggggggag aggcctggac agtaggaaga 780
tcttgcccag ggtcctggat ccgccactct gggggtgacc ttggacaaac ctctgccttg 840
gccctcagtc tccccatcaa ggtttttcca ttcaggaggg tttgggccat cttcagccac 900
cctaccagcc ctgaaaagga tgtgactcct gtttctggga agtgtgtggt gtgttaggtg 960
ggcctacagc cctggttgtg gggagggaag gatggagaga cagcacagt acagagccca 1020
gactgcaggc tggagtggg gttccacttc ccgctgctg tgtgtcctgg accagtgcct 1080
ctgaaccttg gcactgggg cagtggatat taacatctt ccaagcccaa ttcttggggc 1140
atcagggcct ccggtcctct gggagggtggc aggtcctcag attggagatg ccatgggggg 1200
gggagggtgc tctccttttg aggggtatgga agtgagaga ggagtggcct ggcgcagctg 1260
ccgtggttct taggggctgg gcccggggag cccatggggc ttgtgcctag aaagcctggg 1320
ctcctcactg ggggttagat gtgcagactt catgtctccc cagctccagc tctgttctct 1380
ataggtcaag cctccacaat gccagaggcc cagggttagc cccctccagc tccctcctag 1440
atctacagct gcccctttga tgacagcgcc attgagtccc ctgggctggg ggggtcatgc 1500
aggggtgagg cagctgcctg ccgcccgtac tcattgcctg gccaggcagg acacaggctg 1560
gcgggcactg agagtgggg ccacgaaatc cattgtcagg ttaccaggat gaagaaccca 1620
ggctggtcgt ggagtgcagg gcggggcctg ccggaagaat tatgggcact gcagcaggag 1680

ggcagcctgg	gccattagct	cctgatgtca	tcgatttggg	tgaggggaca	gggaagtcag	1740
aggaagctgg	ccagtggctc	tcacgcagac	ttacagcagt	ggagtgggtc	ctgattctctg	1800
gtacagctgc	ccccactgag	tctccaggga	tctgtggttc	aggacccccct	gcaacccccct	1860
cccagacccc	tgtactggtg	ggaggagagg	acctagagga	aagggtgctgg	gcagataagc	1920
agctgaggga	ggccctgggt	ttagcttata	agtcttctgg	gccctcctgc	cccaggaagg	1980
gcagcgagga	ccatgggtgtt	gcccctgtca	tcgttatcgt	cctggccatg	agcttgacgg	2040
actgggaggg	ccggagtcag	ccaggcagac	ggcagcacag	catttgccctg	ttggcaggtg	2100
gccttggtgg	cttcccaaag	gcaatcgctc	cacgcagaac	aaaactcact	tttttggggg	2160
gtgaagcacc	ttggttcatt	tgtttagttc	gttaattcca	gcagtctgtt	tctaagggaa	2220
acatggctgc	agccggctct	gcgcctccca	ccctcccacc	aggtgcccag	tgttcccaag	2280
ggccccgaat	cccaacctta	ttcaggcgctc	agcatctctg	cacccccaat	gcctgttagg	2340
gaggatagtg	aaggctgagc	cctcctgggc	ccatcaaaag	ccagcagtga	gagaacaccc	2400
ccatctctct	gaggtgacct	ctgtagggcag	tccgtgctgt	ctggctggcc	tggtgtgaggt	2460
gggcagggac	caaggcctgg	cgccctgggccc	tcgctggcct	tgctctgctg	gctgacttca	2520
tcctgatagt	accttgattt	tcctactgtg	acttccccct	ctgtcgactt	cctcaccaac	2580
tttaaaattc	cgtattgaga	gcagtttcct	aagttacctc	aaatcctatt	cagaagaagg	2640
ttcttcctgg	aagttgggag	ggcggaaaac	aagtttagtc	acagaagact	actccatgtt	2700
tgagcttctg	tttcaaggga	agttagtaac	tgccggagga	gcctgcccc	tctgcagtgt	2760
gtggtgttgc	cctgatactt	ttcagattga	ggtgttactt	acatgtaata	aatgcacag	2820
acttaagtgt	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa			2860

<210> 56

<211> 1559

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1445)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1551)

<223> n equals a,t,g, or c

<400> 56

atccagcagt	ggggagacag	cgtgctgggc	aggcgtgccc	gagaccttct	cctgcagctc	60
tacctacagc	ggccggagct	gcgggtgccc	gtgctgagg	tcctactgca	cagcgaagg	120
gctgccagca	gcagcgtctg	caagctggac	ggactcatcc	accgcttcat	cacgctcctt	180
gcggacacca	gcgactcccc	ggcgttgagg	aaccgagggg	cgatgccag	catggcctgc	240
cggaagctgg	cgggtggcgca	cccgtgctg	ctgctcaggc	acctgccc	gatcgcgcg	300
ctcctgcacg	gcccgcacca	cctcaacttc	caggagtcc	ggcagcagaa	ccacctgagc	360
tgcttcctgc	acgtgctggg	cctgctggag	ctgctgcagc	cgacagtgtt	ccgcagcgag	420
caccaggggg	cgtgtgggga	ctgccttctg	tccttcaccc	gcctgctgct	gaattacagg	480
aagtctctcc	gccatctggc	tgcttctc	aacaagtttg	tgagttcat	ccataagtac	540
attacctaca	atgccccagc	agccatctcc	ttcctgcaga	agcacgccga	cccgtccac	600
gacctgtcct	tcgacaacag	tgacctgggtg	atgctgaaat	ccctccttgc	agggctcagc	660
ctgcccagca	gggacgacag	gaccgaccga	ggcctggacg	aagagggcga	ggaggagagc	720
tcagccggct	ccttgccctt	ggtcagcgctc	tccctgttca	cccctctgac	cgcggccgag	780
atggccccct	acatgaaacg	gctttcccgg	ggccaaacgg	tggaggatct	gctggaggtt	840
ctgagtgaca	tagacgagat	gtcccggcgg	agaccgaga	tcctgagctt	cttctcgacc	900
aacctgcagc	ggctgatgag	ctcggccgag	gagtggttgc	gcaacctcgc	cttcagcctg	960
gcccctgcgt	ccatgcagaa	cagccccagc	attgcagccg	ctttcctgcc	cacgttcatg	1020
tactgcctgg	gcagccagga	ctttgaggtg	gtgcagacgg	ccctccggaa	cctgcctgag	1080
tacgctctcc	tgtgccaaga	gcacgcggct	gtgctgctcc	accgggctt	cctgggtggg	1140
atgtacggcc	agatggaccc	cagcgcgcag	atctccgagg	ccctgaggat	cctgcatatg	1200

33

gaggccgtga	tgtgagcctg	tggcagccga	ccccctcca	agccccggcc	cgtcccgtcc	1260
ccggggatcc	tcgaggcaaa	gcccaggaag	cgtgggcgtt	gctggctctgt	ccgaggaggt	1320
gagggcgccg	agccctgagg	ccaggcaggc	ccaggagcaa	tactccgagc	cctgggggtg	1380
ctccgggccc	gccgtggca	tcagggggccg	tccagcaagc	cctcattcac	cttctgggccc	1440
acagnccctgc	gcggagcggc	ggatcccccc	gggcatggcc	tgggctgggt	ttgaatgaaa	1500
cgacctgaac	tgtcaaaaaa	aaaaaaaaaa	aaaccgrgg	gggggcccgg	naccaatt	1559

<210> 57

<211> 2064

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (2001)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2024)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2049)

<223> n equals a,t,g, or c

<400> 57

atgggagagg	ctgccccggc	ccggcgcgca	cgccccgacc	tctccccagc	cctggcggtg	60
gcccagcccc	gcccaggcag	caatgggggt	cctgcagctg	ctggctcgtar	cggtgctggy	120
atccgaacac	cgggtggctg	gtgcagccga	ggctctcggg	aattccagcg	arggtcttat	180
tgaattttct	gtggggaaat	ttagatactt	cgagctcaat	aggccctttc	cagagggaagc	240
tattttgcat	gatatattca	gcaatgtgac	ttttcttatt	ttccaaatac	actcacagta	300
tcagaataca	actgtttcct	tttctccgag	gcgtagatcc	cccaccatgt	gacgctggga	360
cagaccagga	ctccagggtg	aggttgcagt	atgatgtcta	tcagtatttt	ctgcctgaga	420
atgacctcac	tgaggagatg	ttgctgaagc	atctgcagag	gatggtcagt	gtgccccagg	480
tgaaggccag	tgctctcaag	gtgggtaccc	taacagctaa	tgataagaca	agtgtttcct	540
tctcctccct	cccgggacaa	ggtgtcatat	acaatgtcat	tgtttgggac	ccgtttctaa	600
atacatctgc	tgcctacatt	cctgctcaca	catacgcttg	cagctttgag	gcaggagagg	660
gtagtgtgtc	ttccctagga	agagtgtctt	ccaaagtgtt	cttcactctt	tttgccctgc	720
ttggtttctt	catttgtttc	tttgacaca	gattctggaa	aacagaatta	ttcttcatag	780
gctttatcat	catgggattc	ttcttttata	tactgattac	aagactgaca	cctatcaagt	840
atgatgtgaa	tctgattctg	acagctgtca	ctggaagcgt	cggtggaatg	ttcttggtag	900
ctgtgtgggtg	gcgatttgga	atcctctcga	tctgcatgct	ctgtgttgga	ctagtgtctg	960
ggttcctcat	ctcgtcagtg	actttcttta	ctccactggg	aaacctaaag	atttttcatg	1020
atgatgggtg	attctgggtc	actttctctt	gcatagctat	cctcattcca	gtagttttca	1080
tgggctgcct	aagaatactg	aacatactga	cttgtggagt	cattggctcc	tattcggtgg	1140
ttttagccat	tgacagttac	tggtccacaa	gcctttccta	catcactttg	aacgtactca	1200
agagagcgct	caacaaggat	ttccacagag	ctttcacaaa	tgtgcctttt	caaactaatg	1260
acttcattat	cctggcagta	tggggcatgc	tggctgtaag	tggaattacg	ttacagattc	1320
gaagagagag	aggacgaccg	ttcttccctc	cccaccata	caagttatgg	aagcaagaga	1380
gagagcgccg	agtgacaaac	attctggacc	ctagctacca	cattcctcca	ttgagagaga	1440
ggctctatgg	ccgattaacc	cagattaag	ggctcttcca	gaaggagcag	ccagctggag	1500
agagaacgcc	tttgcttctg	tagatgcccc	ggggcttggt	cagtgtgcct	cagctttgga	1560
gttcatgcct	ggagtgggtc	aacagctctc	ggtgcaagtc	taataagaga	tcaggcatat	1620
atatctgttc	tttgcataat	attatgggtc	ccttattgat	atatggttaag	ggtgtactag	1680
gggattagga	tgattgtaag	agaatgagaa	agatgaccaa	aaggttggtg	gtagggaggc	1740

34

tttttcttat	ttccaaatac	ttgagaaatt	accttttggg	ttacaaatct	atgatcaact	1800
tattccatta	aatagataca	ttaaaaaat	taaaaactga	ttcttctgca	gagcactggg	1860
gtttcttttt	ataacccctt	gaaacaagtc	tctcacctga	gcctgtctaa	actttcggag	1920
ggagttttatt	attgagtcct	tatctgtgac	agtatttggg	gatttaggga	tttgatactt	1980
aggcctttga	attttagaat	ncaaaaaggg	gagccagcca	gacngggggg	ccaacccgga	2040
tccccaacng	ggaccagggg	ggtc				2064

<210> 58

<211> 1050

<212> DNA

<213> Homo sapiens

<400> 58

ccacgcgtcc	ggccagccag	tccgcccgtc	cggagcccg	ctcgtctggg	cagcatggcg	60
gggtcgccgc	tgctctgggg	gccgcggggc	ggggcgctcg	gccttttggg	gctgctgctg	120
ctcggcctgt	ttcggccgcc	ccccgcgctc	tgccgcgggc	cggtaaagga	gccccgcggc	180
ctaagcgcag	cgtctccgcc	cttggtctaga	ctggcgctcc	tcgccgcttc	cggcggctcag	240
tgccccgagg	tgaggcggcg	ggggcggtgc	agacctggcg	cggcgctgg	cgcatctgct	300
ggagccgaac	gtcaggagcg	ggcgcgggcc	gaggcgagga	ggctgaggat	cagcaggcgc	360
gcgtcctggc	gcagctgctg	cgcgtctggg	gcgccccccg	caactctgat	ccggctctgg	420
gcctggacga	cgaccccgac	gcgcctgcag	cgcagctcgc	tcgcgctctg	ctccgcgccc	480
gccttgaccc	tgccgccta	gcagcccagc	ttgtccccgc	gcccgctccc	gccgcggcgc	540
tccgaccccc	gcccccggtc	tacgacgacg	gccccgcggg	cccggtatgt	gaggaggcag	600
gcgacgagac	accgcagctg	gaccccgagc	tggtgaggta	cttgctggga	cggattcttg	660
cgggaagcgc	ggactccgag	ggggtggcag	ccccgcgccc	cctccgcctg	gccgccgacc	720
acgatgtggg	ctctgagctg	ccccctgagg	gcgtgctggg	ggcgctgctg	cgtgtgaaac	780
gcctagagac	cccggcgccc	caggtgcctg	cacgcgcctt	cttgccaccc	tgagcactgc	840
ccggatcccc	tgacacctgg	gacccagaag	tgcccccgcc	atcccgccac	caggactgct	900
ccccgccagc	acgtccagag	caacttacc	cggccagcca	gcctctcac	ccgaggatcc	960
ctacccccctg	gccccacaat	aaacatgatc	tgaagcagca	aaaaaaaaaa	aaaaaaaaaa	1020
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa				1050

<210> 59

<211> 2533

<212> DNA

<213> Homo sapiens

<400> 59

ccacgcgtcc	gcctggcaac	ccctaataatt	tgggatctct	caatgctatt	tgccctcatt	60
agcttgctcg	ttatgcttcc	cacttggtgg	attgtgtctt	cctggctggg	atggggagtg	120
attctatttg	tgtatctggg	cataagagct	ttgagattat	ggaggacagc	caaactacaa	180
gtgaccctaa	aaaaatacag	cgttcatttg	gaagatatgg	ccacaaacag	ccgagctttt	240
actaacctcg	tgagaaaagc	tttacgtctc	attcaagaaa	ccgaagtgat	ttccagagga	300
tttacctggg	tcagtgtctg	ttgccatttt	aataaagctg	gacagcatcc	aagtcagcat	360
ctcatcggtc	ttcgaaagc	tgtctaccga	actctaagag	ccaacttcca	agcagcaagg	420
ctagctaccc	tatatatgct	gaaaaactac	cccctgaact	ctgagagtga	caatgtaacc	480
aactacatct	gtgtgggtgc	ttttaaagag	ctgggccttg	gacttagtga	agagcagatt	540
tcagaagagg	aagcacataa	ctttacagat	ggcttcagcc	tgccctgcatt	gaaggttttg	600
ttccaactct	gggtggcaca	gagttcagag	ttcttcagac	ggttagccct	attactttct	660
acagccaatt	cacctcctgg	gcccttactt	actccagcac	ttctgcctca	tcgtatctta	720
tctgatgtga	ctcaaggctt	acctcatgct	cattctgcct	gtttggaaga	gcttaagcgc	780
agctatgagt	tctatcggtg	ctttgaaact	cagcaccagt	cagtaccgca	gtgtttatcc	840
aaaactcaac	agaagtcaag	agaactgaat	aatgttcaca	cagcagtgcg	tagcttgcat	900
ctccatctga	aagcattact	gaatgaggtg	ataattcttg	aagatgaact	tgaaaagctt	960
gtttgtacta	aagaaacaca	agaactagtg	tcagaggctt	atcccatcct	agaacagaaa	1020
ttaaagtgtg	ttcagcccca	cgttcaagca	agcaacaatt	gctgggaaga	ggccatttct	1080

35

caggctcgaca	aactgctacy	aagaaatata	gataaaaaag	gcaagcctga	aatagcatgt	1140
gaaaacccac	attgtacagt	aagtaccttt	gaagcagcct	actctacaca	ttgcagacaa	1200
agatccaate	ccagaggagc	aggaattaga	agcttatgta	gatgatatag	atattgatag	1260
tgatttcaga	aaggatgatt	tttattactt	gtctcaagaa	gacaaagaga	gacagaagcg	1320
tgagcatgaa	gaatccaaga	gggtgctcca	agaattaaaa	tctgtgctgg	gattttaaagc	1380
ttcagaggca	gaaaggcaga	agtggagca	acttctattt	agtgatcatg	tgtttcttca	1440
tatagcttta	aaattatgct	attgacatta	tgggaaagat	ttatcaatga	gagaaatgtg	1500
tctctttttc	agccgtgttg	aaatccttgt	ctcctgtaga	cccagtggaa	cccataagta	1560
attcagaacc	atcaatgaat	tcagatatgg	gaaaagtcag	taaaaatgat	actgaagagg	1620
aaagtaataa	atccgccaca	acagacaatg	aaataagtag	gactgagtat	ttatgtgaaa	1680
actctctaga	aggtaaaaaat	aaagataatt	cttcaaatga	agtcttcccc	caaggagcag	1740
aagaaagaat	gtgttaccaa	tgtgagagtg	aagatgaacc	acaagcagat	ggaagtggtc	1800
tgaccactgc	ccctccaact	cccagggact	cattacagcc	ctccattaag	cagaggctgg	1860
cacggctaca	gctgtcacca	gattttacct	tactgctgg	ccttgctgca	gaagtggctg	1920
ctagatctct	ctcctttacc	accatgcagg	aacagacttt	tgggtgatgag	gaggaagaac	1980
aaataataga	agaaaataaa	aatgagatag	agaaaaagta	agaaccaaga	ttcatatgaa	2040
gtgatattag	attgttcctt	ttacaaaagt	gtttagcttc	aagactggaa	agggaaatag	2100
agtgtaaagt	tactatatat	aaagctaaga	tgtggattta	caggaagaac	cctgggttga	2160
ataactgatc	tgaaattagt	agttacctgt	aaatggcaga	tcttttagga	aaataagaga	2220
aaggtaaggg	ctcttttgaa	taaactgctg	ttttatttgt	ggcacactg	atcaatcttg	2280
gaaattcttt	aagtattttt	aataagaaat	gaattatcat	ttcttgccag	aatttgctac	2340
cttaaggtga	ttgggaaaat	tctgttgcaa	gaacattaac	atttagtatg	actccttttt	2400
actgtattct	tgcagttaat	aactgcagct	attatgttaa	taacaagttg	tttgtatttt	2460
atttttgttt	ataccagtct	taaagatcca	ggttctgaat	aaaaaaatta	attgatacaa	2520
aaaaaaaaaa	aaa					2533

<210> 60

<211> 899

<212> DNA

<213> Homo sapiens

<400> 60

ggcagatttc	ccggcacctt	cgtgggcacc	acagagcccg	cctccccacc	cctgagcagc	60
acctcaccac	ccactgctgc	ggccactatg	cctgtgtgtg	cctctgtggc	cagcctggcc	120
cctccggggg	aggcctcgct	ctgcctggaa	gaggtggccc	cccctgccag	tgggaccgcg	180
aaagctcggg	tgctctatga	ctacgaggca	gccgacagca	gtgagctggc	cctgctggct	240
gatgagctca	tactgtctta	cagcctgcct	ggcatggacc	ctgactggct	cattggcgag	300
agaggcaaca	agaagggcaa	ggtccctgtc	acctacttgg	aactgctcag	ctaggcaggt	360
gcccccatcc	cccccgcat	ctggcctagg	caggagagga	tgggcgcact	gccacttaac	420
ttgtttgttg	gtgacacagt	tgttcagagt	ggggagaatt	cacccccatt	tgtccctgcc	480
cctagtcacc	tagctgtgag	ggtgcctgag	gctgaatggc	tccaccctcc	cccagccctg	540
cttctgacct	gtggctctgg	agcccctgcc	cctgcctgca	tccccgagca	ccccaccctc	600
caggctccac	taaggaggga	ggggctgtct	gcagcagctg	cactcagcac	ctaggccagg	660
gtggggccgc	cgcagatggg	ctcaggaagc	cccaggtgca	ctcagcgaga	gccctgcctt	720
tcagttgcc	aaagctgcat	caggggaatg	cggcaaggca	cacagggtc	tggcagcccc	780
tggggactgg	gcgctgcccc	tgggagggga	gagcctggcc	agggctgggt	ttggggcccg	840
agcagcatct	tccggtgcta	tcctcccctc	ccaccctca	cagctcaagc	caagtccag	899

<210> 61

<211> 1079

<212> DNA

<213> Homo sapiens

<400> 61

tcgacccacg	cgctccgggt	tcaccacgtt	ggccaggctg	gtctcaaact	cctgacttca	60
ggttgccctc	caaagtgcgt	ggattaaagg	catgagccac	tgcgccccgc	ctacctttct	120

aactctactt	ctagcttctt	gcttctgggc	tgctgctata	ccaaacagga	atgtaatact	180
ttctgtcagc	ttcaggcctt	tgcacatgca	gttcactttg	tctatcttgg	tttttattct	240
taggattttaa	attctcctaa	gaagctttct	ctgaccagcc	taaaacttac	gtaagccctg	300
ggtaggtgc	tatgcttatg	tcctcccata	gcattttgca	tttgcatgtg	ttgtaactct	360
taatgtacag	catcatgatt	gcctatttta	actttctgt	ttgttacagt	agactttaat	420
ctctttaagg	acaggaaactg	tgtcttgttt	agaatcccca	gagcttattt	agtacaatgg	480
ctatgcttat	aattttaagta	tttattgaac	aaatgaaatt	ttcctaagcc	ctaaaacctt	540
gcaagatgtt	ttagtgagg	aaactggcct	cggtggagtt	gaataactag	cacgagggtca	600
ctcacctaaa	aagtggtag	gagggattaa	aatctaaatc	tgtttagctg	ttaaagattgg	660
gcttttttgc	ttgctgctgc	acatgactgc	ytctctcat	gttgccctga	cacatccctg	720
tcaagtgttc	aaacagccc	tgccatacaa	ccccatccat	agcttctgag	gaaagtgtgtg	780
tcactcttgg	acagctctga	gagctgaagc	gagctcttgc	agaataattt	cccatctatt	840
ggctcttaatt	tatgctttgg	agaatataac	ttattttcaa	aaaacaaatg	attcagaatt	900
tgctatctcc	ttaagggtccg	tttattagtt	tatttctatc	cttcattcac	tgataacccat	960
ttactgagca	ccagcctggg	caacatgggtg	agaaccatc	tctaccaatt	taaaaaaaaaa	1020
aaaaaagggc	ggccgctcta	gaggatccaa	gcttacgtac	gcgtgcatgc	gacgtcata	1079

<210> 62

<211> 1928

<212> DNA

<213> Homo sapiens

<400> 62

ggcagcagag	taggtctgcc	ggcgatggag	tggtgggcta	gctcgccgct	tcggctctgg	60
ctgctgttgt	tcctctgcc	ctcagcgcag	ggccgccaga	aggagtcagg	ttcaaaatgg	120
aaagtattta	ttgaccaa	taacaggctc	ttggagaatt	acgaaccatg	ttcaagtcaa	180
aactgcagct	gctaccatgg	tgcatagaa	gaggatctaa	ctcctttccg	aggaggcatc	240
tccaggaaga	tgatggcaga	ggtagtcaga	cgaagctag	ggaccacta	tcagatcact	300
aagaacagac	tgtagccgga	aaatgactgc	atgttcccct	caaggtgtag	tggtgttgag	360
cactttattt	tggagtgat	cgggcgctc	cctgacatgg	agatgggtgat	caatgtacga	420
gattatcctc	agggttcctaa	atggatggag	cctgccatcc	cagtcttctc	cttcagtaag	480
acatcagagt	accatgatat	catgtatcct	gcttggacat	tttgggaagg	gggacctgct	540
gtttggccaa	tttatcctac	aggtcttggg	cggtgggacc	tcttcagaga	agatctggta	600
aggctcagcag	cacagtggcc	atggaaaaag	aaaaactcta	cagcatattt	ccgaggatca	660
aggacaagtc	cagaacgaga	tcctctcatt	cttctgtctc	ggaaaaaccc	aaaacttggt	720
gatgcagaat	acaccaaata	ccaggcctgg	aaatctatga	aagatacctt	aggaaagcca	780
gctgctaagg	atgtccatct	tgtagtcac	tgcaaatata	agtatctgtt	taattttcga	840
ggcgtagctg	caagtttccg	gtttaa	ctcttctgt	gtggctcact	tgtttccat	900
gttggtgatg	agtggctaga	attcttctat	ccacagctga	agccatgggt	tcactatata	960
ccagtcacaa	cagatctctc	caatgtccaa	gagctgttac	aatttgtaaa	agcaaatgat	1020
gatgtagctc	aagagattgc	tgaaggggga	agccagttta	ttaggaacca	tttgcagatg	1080
gatgacatca	cctgttactg	ggagaacctc	ttgagtgaat	actctaaatt	cctgtcttat	1140
aatgtaacga	gaaggaaagg	ttatgatcaa	attattccca	aaatgttgaa	aactgaacta	1200
tagtagtcat	cataggacca	tagtctctct	tgtggcaaca	gatctcagat	atcctacggt	1260
gagaagctta	ccataagctt	ggcacctata	ccttgaatat	ctgctatcaa	gccaaatacc	1320
tggttttcc	tatcatgctg	caccagagc	aactcttgag	aaagatttaa	aatgtgtcta	1380
atacactgat	atgaagcagt	tcaacttttt	ggatgaataa	ggaccagaaa	tcgtgagatg	1440
tggattttga	acccaactct	acctttcatt	ttcttaagac	caatcacagc	ttgtgcctca	1500
gatcatccac	ctgtgtgagt	ccatcactgt	gaaattgact	gtgtccatgt	gatgatgcc	1560
tttgtcccat	tatttgagc	agaaaattcg	tcatttgga	gtagtacaac	tcattgctgg	1620
aattgtgaaa	ttattcaagg	cgtgatctct	gtcactttat	tttaatgtag	gaaacctat	1680
ggggtttatg	aaaaatactt	ggggatcatt	ctctgaatgg	tctaaggaag	cggtagccat	1740
gccatgcaat	gatgtaggag	ttctcttttg	taaaaccata	aactctgtta	ctcaggaggt	1800
ttctataatg	ccacatagaa	agaggccaat	tgcatgagta	attattgcaa	ttggatttca	1860
ggttcccttt	ttgtgccttc	atgcctact	tcttaatgcc	tctctaaagc	caaaaaaaaaa	1920
aaaaaaaa						1928

<210> 63

<211> 781

<212> DNA

<213> Homo sapiens

<400> 63

ggcagcagat	tttcagcctt	tttggactgg	tttctccaca	tcttcgtgga	tttatctaac	60
tttggctctt	gatgttggtg	accttcagat	tgggtctctg	agtgaacatc	ctttttgttg	120
atgttgatac	tattcctttc	tgtttggttg	tttgttttcc	ttctaacagt	cagggccctc	180
tgctgcaggt	ctgctggagt	ttggttgagg	tccactccag	accctgtttg	tctgggtttt	240
gccagaggag	gctgcagaat	agcaatgatt	gctgcctgtt	tttcctctgg	aagctttgtc	300
ccagaggggc	accaccaga	tgccagccag	agctctcctg	tatgagggtg	ctgttggtcc	360
atacttgag	gtgccttcca	gtcaggatac	acagggtgtc	ggtaccact	tgaggaggca	420
ctctgtcccc	tatcagagct	cgaacactgt	gctgggagat	ccactgttct	cttcagagct	480
gtcagacagg	gacgtttaag	tctgctgaag	ctatgtccac	agctgccctc	ttccccagat	540
gctctgtccc	agggagaagg	gagttttatc	tataagtctc	tgactggggc	tgctgccttt	600
tcttcagaga	tgccctgccc	caagacgggg	actctagaga	ggcagctctg	ctgcagtggt	660
cttgctgaac	tgtggtgggc	ttcaccaggt	tggaccttcc	ctgagccttt	ttttttaccc	720
tgtgagggtg	aaaatgccta	atcaagcctc	agcaatgggt	gatgcccttc	ccccaccac	780
g						781

<210> 64

<211> 1194

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1172)

<223> n equals a,t,g, or c

<400> 64

ggcagcagaa	gacatggagt	cttaagtgtg	atcagtgagg	gggggctgga	atcatttaga	60
ggcatcttca	ttcacaaaac	caggagctga	tactggctgt	cagccaggac	ttcaactgac	120
ctatgtagaa	cctgtccatg	tggcccctcc	ttgcagcttc	cccatattgg	ctggtttggg	180
cttcatcaca	gtccggcagc	ttactttctaa	gggcaagcat	tccacgacaa	cacagcagaa	240
gggcatggca	tttttacagt	gaagtttggc	aatctcatag	cgctgcttct	gtcctacttt	300
atattattgt	cagggcaatc	acaaagatgt	gcataaggct	aaagaaaaga	gacataaccc	360
cgaccacgcg	atggaagaag	tgacacggtc	atgttatgag	aggagtgtgt	gggatgggag	420
atagggtgtg	ggccacctgc	agaaaacagc	atctgctata	ggctgtcatg	gaagcgcagg	480
atggggattt	agcctacctg	aggggtcagt	cagcaaaggc	ctctgggagg	aagtgcagac	540
ttcggtctgag	gatgtgaagg	gctaaaagga	gaatgaggaa	gagtttcagg	gagagggaatc	600
aatgaaaacga	gtccagagac	gctggtgagt	tggatggttt	gcttcagtat	gatgacaata	660
cagaggggca	aggagactgg	tgaggagaaa	gagagaaggt	gccatgtgct	ctgggtcgtg	720
tcttctatgc	cagactccct	tagaagagga	gcagcctcca	gtcagcgggt	tcccagggaac	780
acggagggcta	gacaggacaa	tggcagccaa	tcctgtctcc	caaactgggt	acagtggggg	840
aaagctgcat	ggtctagatc	caccctgtct	cctggcccca	gtatagaaga	tcaaattcaa	900
tctgcccatt	cttatccaga	taaagtaaa	gaagactgga	aaaaagaact	aatccacggc	960
tccatctgcc	catgactttc	tctgctgatg	ccggaggcag	ctatggataa	agagacggca	1020
cacggcatgt	cccgcagctg	tggaggtggg	gagaccccgc	aagtccacag	gaaaagagtt	1080
aagttgctgc	cacctgggca	tccgctattc	tctgctcttc	tgctcatccc	tcaattcaga	1140
ccatgatgga	gctgattgtc	tcccatttta	tnccttggat	tgaatgggtc	cgag	1194

<210> 65

<211> 1677

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1012)

<223> n equals a,t,g, or c

<400> 65

gggtgcagtgg	tgccatcaca	gttcaactgca	gccttgacct	cccgggctca	agcaatcctc	60
ccacctcagc	cacttgagta	gctgagacct	cagatatgtg	ccatcacacc	cagctgattt	120
tttaaaatta	atTTTTtga	gagatagggt	ctcatatgtt	gcccagctg	gtctcaaaact	180
actgggttca	aatgatcctc	ctgcctcagc	cttccaaaagt	actgggatta	caggcatgag	240
ccaccatgcc	gggctgggag	gcggaatttt	gttcagtcta	aagataagct	ttttcatagc	300
tctggctgta	gtgggagggg	gcagaggagt	gaatgattgt	cagttgggag	gggtgcagagt	360
gggctcctgc	cctagggtgr	aggtraggg	ggcttaggtg	asmcamcaca	gaggccctgt	420
tcagccccac	gtccccctcc	tgtgctcctc	cctcctctct	cctcctcctg	aggcgtggga	480
ggatatcatca	ttcagcagat	ttcaccagag	gcagtggagg	aggcaggtag	ctgagccaga	540
attcagaatg	tcttattctc	cacttgactc	tgccactaac	ttgttgtgca	actttgggcc	600
tttccccagg	ccttcatttt	cttttctttt	cttttctttt	yttttttttt	gaggcggagt	660
ctcgctatgt	tgcccagggt	ggagtgcagt	ggcgagcat	catctcggct	cactgcaagc	720
tccaccttct	gagttcacgc	cattctactg	cctcagcctc	ccgagtagcc	gggactgcag	780
gcrccccacca	ccacgcccgg	cttatttttt	gtatttttag	tagagacagg	gtttcaccac	840
gtagccaag	atgggtctga	tctcctgacc	tcgtgatcca	cccgcctggg	cttcccaaaag	900
tgctgggatt	acaggcgtga	gccactgcgc	ccggccattt	tcttaaatat	ctaataaaaa	960
atatatagca	aatgcagttt	ttaaactacg	acaatatgac	cacgcaaaag	antattatct	1020
tccaagactg	ctgggtccaag	gaaaagtcag	taataaagtg	gaagcattgt	agcttatgga	1080
atgactgggt	asatttgga	gaagccttag	caataatcta	gaatctgcat	agataataca	1140
tctgaggatt	gggctttgtg	gtttacaaaag	catttttttt	tcctcttttg	atcccagccg	1200
tttgcttgga	ctgatacaaa	gcatttttat	tagtttgtct	tattcaatcc	tcacaccacc	1260
tcaaattttac	agaggatatg	gatctgggta	atttgtatga	ctatgtaacc	tcagtgcagt	1320
ccacagcact	gcctggagg	gggtagagg	ggctcctggg	tggaatccca	gccccagtg	1380
gaccttgagc	aagttacttt	agctgtctgc	acctaaattt	cctcactggc	aaaacaggaa	1440
tactggtggt	tcacacctgc	aattccagca	ctttgggagg	ctgaggtggg	aggattgctt	1500
gagtcagaa	gttcaaaacc	agactgggca	acatagcaag	accatctcta	caaaaaattaa	1560
ataataaaaa	catttacaag	ggtgtgtgtg	aagattaaat	gagatcactc	acgaaaaagc	1620
tcagcagacc	ctgatgtgca	gtagggtgctc	aataaatgtt	agccagcaaa	aaaaaag	1677

<210> 66

<211> 1237

<212> DNA

<213> Homo sapiens

<400> 66

agcaaaccce	ggaaggtgtg	gcgtccccgc	ttcgcgccaa	gatggtgctg	gtgctgcgcc	60
atcctttgtg	tgccccggaa	agggcggtcc	gggagccggg	tcgggggctc	ctgactcgca	120
ctgggcagca	tgacgggtgc	ccggctgtca	ctgctgtgcc	gggacctctg	ggcgctgtgg	180
ctgctgctga	aggccggcgc	agtgcgtggg	gcgcggggcg	gtcctcgcc	ccccggaagg	240
tggtgtgggg	cgacatgcgg	ggacgcgggg	cgggggtgga	cgttctgggc	ccagccctgt	300
cctcagaagc	tgctggggca	gaagcccggg	gctgggggat	gccggggatg	gggtgtgggg	360
tggtgtgcctc	cgagaccaga	ggagccctgt	tccttgccag	ggaaggtgtg	cacgggcctt	420
gcccgatgga	tggtttaggg	ccatggccct	gggtccctg	gtgagcagtg	gggcccctc	480
tgcccttgcc	ctgtgaggga	ctgtctgtgc	tggtcccaga	aggctgggat	cacctttcca	540
ctggctcctt	tggtcgaggt	ttttcataga	caggctatgt	ggacaaatga	gggcagcgcc	600
cacgtctggc	tggtggagg	gctgcggctc	ctccttgag	gggacgcctg	gccactgctg	660
tccccacaat	ggggccaccc	gtggtgcaag	gcgtgacaag	ctgcctctc	taggtaagca	720
ggacttgga	ggcccctggc	caagcctgtg	gaccgcggctg	ggcggcctct	gtggtctcag	780

39

gtttgggtgt	gtttgggtctg	gtcagggctc	aggggctgct	ggccacact	ggccccatcc	840
tgacaattgg	agcttttggg	caaggctcc	ggagaagggg	tcacgtcggg	aggaaacagc	900
ctgggttttg	ttgatgcttt	tctaagaatg	gagtactcgt	tttcaagaga	tttgtcttaa	960
ttatatatttc	cagcgggtac	ttatgccaa	tattgatgaa	taattcataa	aataagcatc	1020
tttgtgaatt	ttagtgaatc	agaccttaac	tatcaacggc	aatgaatgaa	catctaaagt	1080
ttccaatttt	aaagtaaaga	actggctggg	tacagcagtt	cacgcctgta	atccccagc	1140
tttgggaggc	caaggctaga	ggatcgcttg	agcccaggag	tttgagatca	gcctgggcaa	1200
cataccaaga	cctcatctgt	taaaaaaaaa	aaaaaaa			1237

<210> 67

<211> 1934

<212> DNA

<213> Homo sapiens

<400> 67

ccacgcgtcc	ggggcggtcc	tggtcgtgag	aggggagccc	caggggagct	ggggcagcat	60
gactgggggtg	ataaatggcc	ggaaatttgg	cgtggccaca	ctcaacacca	gcgtgatgca	120
ggaggcacac	tccgggttca	gcagcatcca	cagcagcatc	cgccatgtcc	cagcaaacgt	180
ggggcctctg	atgcgggtgc	tcgtggtcac	catcgcccc	atctactggg	ccctggccag	240
agagagtggg	gaagccctga	atggccactc	tctgactggg	ggcaagtacc	ggcaggagtc	300
acacgtggag	tttgctacag	gggagctgct	cacgatgacc	cagtggcccc	gggtctggat	360
cccgatggcc	tcctgctcct	cgacgtgggtg	gtcaatggcg	ttgtccccgg	acagcctggc	420
tgacgcagat	cttcaagtgc	aggactttga	ggagcactac	gtgcaaacag	ggcctggcca	480
gctgttcgtg	ggctccacac	agcgcttctt	ccagggcggc	ctccccctgt	tcctacgctg	540
caaccacagc	atccagtaca	acgcggcccc	ggggccccag	ccccagctgg	tgcagcacct	600
gcgggcctca	gctatcagct	cggcctttga	tccagaggcc	gaggccctgc	gcttccagct	660
cgctacagcc	ctgcaggcgg	aggagaacga	ggtcggctgc	cccaggggct	ttgagctgga	720
ctcccaggga	gcgttttgtg	tggatgtgga	cgagtgtgcg	tgggatgtct	acctctgccg	780
agagggacag	cgctgtgtga	acctgtctcg	gtcctaccgc	tgctccccg	actgtgggcc	840
tggcttccgg	gtggctgatg	gggcccggctg	tgaagatgtg	gacgaatgcc	tggagggggtt	900
ggacgactgt	cactacaacc	agctctgcga	gaacacccca	ggcggtcacc	gctgcagctg	960
cccaggggt	taccggatgc	agggccccag	cctgccctgc	ctagatgtca	atgagtgcct	1020
gcagctgccc	aaggcctgcg	cctaccagtg	ccacaacctc	cagggcagct	accgctgcct	1080
gtgccccca	ggccagaccc	tccttcgcga	cggcaaggcc	tgcaacctac	tggagcggaa	1140
tggacaaaat	gtgaccaccg	tcagccaccg	aggccctcta	ttgccctggc	tgcgcccttg	1200
ggcctcgatc	ccccgtacct	cctaccacgc	ctgggtctct	ctccgtccgg	gtcccatggc	1260
cctgagcagt	gtgggcccgg	cctggtgccc	tcctggtttc	atcaggcaga	acggagtctg	1320
cacagacctt	gacgagtgcc	gcgtgaggaa	cctgtgtcag	cacgcctgcc	gcaaacactga	1380
gggcagctac	cagtgcctgt	gccccgccgg	ctaccgtctg	ctccccagcg	ggaagaactg	1440
ccaggacatc	aacgagtgcg	aggaggagag	catcgagtgt	ggacccggcc	agatgtgctt	1500
caacacccgt	ggcagctacc	agtgtgtgga	cacacctgt	cctgccacct	accggcaggg	1560
ccccagccct	gggacgtgct	tccggcgctg	ctcgcaggac	tgcggcacgg	gcggcccttc	1620
tacgctgcag	taccggctgc	tgccgctgcc	cctgggcgtg	cgcgccacc	acgacgtggc	1680
ccgcctcacc	gccttctccg	aggtcggcgt	ccccgccaac	cgcaccgagc	tcagcatgct	1740
ggagcccgac	ccccgcagcc	ccttcgcgct	gcgtccgctg	cgcgcgggcc	ttggcgcggt	1800
ctacacccgt	cgcgcgtca	cccgcgccgg	cctctaccgg	ctcaccgtgc	gtgctgcggc	1860
accgcgccac	caaagcgtct	tcgtcttgct	catcgccgtg	tccccctacc	cctactaaac	1920
gggagagggc	attg					1934

<210> 68

<211> 3300

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (3)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (15)

<223> n equals a,t,g, or c

<400> 68

ncngcagccg	gacgnccgag	cgcagcgagt	cagtgcgga	ggaagcggaa	gagcgcccaa	60
tacgcaaacc	gcctctcccc	gcgcgttggc	cgattcatta	atgcagctgg	cacgacaggt	120
ttcccagactg	gaaagcgggc	agtgcgcca	acgcaattaa	tgtgagttag	ctcactcatt	180
aggcacccca	ggctttacac	tttatgcttc	cggtctgtat	gttgtgtgga	attgtgagcg	240
gataacaatt	tcacacagga	aacagctatg	accatgatta	cgccaagctc	gaaattaacc	300
ctcactaaaag	ggaacaaaag	ctggagctcc	accgcggtgg	cgcccgctct	agaactagt	360
gatcccccg	gctgcaggaa	ttcggcacga	gaacacatct	taagggaacc	aagtctcaag	420
agaaatcaag	taattatgaa	tgaacagctc	taaaaaagag	agagagaata	ttttcttaaa	480
tcaacttagt	tgctgttatg	accaaagaac	agatgttgtg	gtgttcaccc	cagagaagca	540
agagattttc	ccttaaacct	cagcttataa	tgaatggaag	tgaatgacag	ggagagagtt	600
tttctctcgt	ttcccagaac	tctatccttt	tctttctcaa	cagttggaaa	ctgtagccaa	660
tacagtagac	agtgcgatgg	gagaaccaa	tcgtcatcca	agcatgtttc	tcttactttt	720
ggtgttggag	agactctacg	cttccccgat	ggatggtact	tcttctgtct	tcagcatggg	780
accttttgtt	cccttcatta	tgaggtgtgg	tcactcacct	gtctaccact	cccgtgaaat	840
ggcagctcgt	gccttgggtcc	catttgttat	gatagatcac	attcctaata	ccattcgaac	900
tctgttgtcc	acactcccca	gctgcactga	ccagtgtttc	cggcaaaacc	acattcatgg	960
gacactttct	caggtttttc	atttgttgca	agcctactca	gactccaaac	acggaaacgaa	1020
ttcagacttc	cagcacgagc	tgactgcacat	cactgtttgt	accaaagcca	aactctggct	1080
ggccaagagg	caaaatccat	gtttgttgac	cagagctgta	tatatgtata	ttctcttctt	1140
attgacttgc	tgctcaaca	gatctgcaa	ggacaaccag	ccagtctctg	agagtctttg	1200
cttctgggag	gaagtcagag	ggattatctc	aggatcagag	ctgataacgg	gattcccttg	1260
ggccttcaag	gtgccaggcc	tgccccagta	cctccagagc	ctcaccagac	tagccattgc	1320
tgagtggtg	gcccgcggcag	ccaagagtgg	agagcgggag	acgaatgtcc	ccatctcttt	1380
ctctcagctg	ttagaatctg	ccttccctga	agtgcgctca	ctaactctgg	aagccctctt	1440
ggaaaagtgc	ttagcagcag	cctctggact	tgagagagaag	ggcgtgccac	ccttgctgtg	1500
caacatggga	gagaagtctt	tattgttggc	catgaaggaa	aatcaccacg	aatgcttctg	1560
caagatactg	aaaattctcc	actgcagtga	ccctggtgag	tggttcccc	agacggagca	1620
ctgtgtccat	ctgaccccaa	aggagtctct	gatctggacg	atggatattg	cttccaatga	1680
aagatctgaa	attcagagtg	tagctctgag	acttgcttcc	aaagtcattt	cccaccacat	1740
gcagacatgt	gtggagaaca	gggaattgat	agctgctgag	ctgaagcagt	gggttcagct	1800
ggtcatcttg	tcatgtgaag	accatcttcc	tacagagtct	aggctggccg	tcgttgaagt	1860
cctcaccagt	actacaccac	ttttctcac	caaccccat	cctattcttg	agttgcagga	1920
tacacttgct	ctctggaagt	gtgtccttac	ccttctgcag	agtgcaggagc	aagctgttag	1980
agatgcagcc	acggaaaccg	tgacaactgc	catgtcaca	gaaaatacct	gccagtcaac	2040
agagtttgcc	ttctgccagg	tggtgcctc	catcgctctg	gccctggccc	tgcccgctct	2100
gtgtgatctg	ctccagcagt	gggaccagtt	ggccccgga	ctgcccaccc	tgctgggag	2160
gctgttggga	gagagtgatg	acctcgtggc	ctgtgtggag	agcatgcac	aggtggaaga	2220
agactacctg	tttgaaaaag	cagaagtcaa	cttttgggcc	gagaccctga	tctttgtgaa	2280
atacctctgc	aagcacctct	tctgtctcct	ctcaaagtcc	ggctggcgct	ccccaaagccc	2340
tgagatgctc	tgctcacctc	aaaggatgg	gtcagagcag	tgccacctcc	tgtctcagtt	2400
cttcagagag	cttccaccag	ctgctgagtt	tgtgaagaca	gtggagttca	caagactacg	2460
cattcaagag	gaaaggactt	tggtctgctt	gaggctgctg	gccttttttg	aaggaaagga	2520
aggggaagac	accctagttc	tcagtgtttg	ggactcttat	gcagaatcga	ggcagttaac	2580
tcttccaaga	acagaagcgg	catgttgaag	aaaatctggg	ggattgggat	gggggtatgt	2640

41

gtggattttt	cctccactaa	atctgcagga	aacatgttga	acataaatc	aaaaatttta	2700
tcccaaaaaa	aaaaaaaaaa	aaactcgagg	gggggcccgg	taccaaatc	gccctatagt	2760
gagtcgtatt	acaattcact	ggccgtcggt	ttacaacgtc	gtgactggga	aaaccctggc	2820
gttaccacaac	ttaatcgcc	tgccagcacat	cccccttccg	ccagctggcg	taatagcgaa	2880
gaggccccga	ccgatcgccc	ttcccaacag	ttgcgcgacc	tgaatggcga	atggcgaatc	2940
gtaagcggtta	atattttgtt	aaaattcgcg	ttaaattttt	gttaaatacag	ctcatttttt	3000
aaccaatagg	ccgaaatcgg	caaaatccct	tataaatcaa	aagaatagac	cgagataggg	3060
ttgagtgttg	ttccagtttg	gaacaagagt	ccactattaa	agaacgtgga	ctccaacgtc	3120
aaagggcgaa	aaaccgtcta	tcagggcgat	ggccactac	gtgaaccatc	accctaatac	3180
agtttttttg	ggtcgagggt	ccgtaaagca	ctaaatcgga	accctaaagg	gagccccga	3240
tttagagctt	gacggggaaa	gccggcgaa	gtggcgagaa	aggaaggga	gctgtctctt	3300

<210> 69

<211> 1797

<212> DNA

<213> Homo sapiens

<400> 69

ggtcgacggt	atcgataagc	ttgatatcga	attcctgcaa	cagttcttgg	aaaccactc	60
gagagggcca	cgctccatt	caccaggcca	cgcatacaaa	gaggcaaac	caggagccaa	120
catgagctcg	gggactgaac	tgctgtggcc	cggagcagcg	ctgctggtgc	tggtgggggt	180
ggcagccagt	ctgtgtgtgc	gctgtctacg	cccagggtga	aagagggtcag	agaaaaacta	240
ccagcagaga	agtctgcgtg	aggaccaaca	gagctttacg	gggtccccga	cctactcctt	300
ggtcgggcag	gcatggccag	gacccctggc	ggacatggca	cccacaagga	aggacaagct	360
gttgcaattc	tacccagcc	tggaggatcc	agcatcttcc	aggtaccaga	acttcagcaa	420
aggaagcaga	cacgggtcgg	aggaagccta	catagacccc	attgccatgg	agtattacaa	480
ctggggggcg	ttctcgaagc	cccagaaga	tgatgatgcc	aattcctacg	agaatgtgct	540
catttgcaag	cagaaaacca	cagagacagg	tgccagcag	gagggcatag	gtggcctctg	600
cagaggggac	ctcagcctgt	cactggccct	gaagactggc	cccacttctg	gtctctgtcc	660
ctctgcctcc	ccggaagaag	atgaaggaat	ctgaggatta	tcagaacttc	agcattccat	720
ccattcagtg	gcgcgagtc	aggaaggtca	tggggcaact	ccagagaaga	aagcatcccc	780
tggccccgtg	ggaagcccag	acgaggagga	cggggaaccg	gattacgtga	atggggaggt	840
ggcagccaca	gaagcctagg	gcagaccaag	aagaaaggag	ccaaggcaaa	gagggaccac	900
tgtgtcctat	gaccatcgc	tgcccttcaa	ggaccatttc	ccagagctac	tcaactttta	960
agcccctgcc	atggttgctc	ctggaaggag	aaccagccac	cctgaggacc	acctggccat	1020
gcgtgcacag	cctgggaaaa	gacagttact	cacgggagct	gcaggccccg	tcaccaagcc	1080
ctctcccagc	ccaggctttg	tggggcaggc	acctggtacc	aagggttaacc	cggctcctgg	1140
tatggacgga	tgcgaggat	ttaggataag	ctgtcaccca	gtccccataa	caaaaccact	1200
gtccaacact	ggtatctgtg	ttctttttgt	ctatgaattt	ggattcctaa	ttgctattgt	1260
tggttgctgg	ggttttaaat	gattgataag	ctgttacagt	taacttatag	agggggagcc	1320
atatttaaca	ttctggattt	cagagtagag	atttctgtgt	tgtctcctag	aaagcattac	1380
atgtagttta	tttcagcatc	ctgtttgggt	ggggccctgg	ctctcttccc	ctttgtgggg	1440
acctccccct	tctttgggct	tcagtttact	caggaagaaa	tgaggctgtc	gccatcttta	1500
tgtgtctcca	gtggaaatgt	cacttgctac	agacaatagt	gcatgagagt	ctagagaagt	1560
agtgaccaga	acagggcaga	gtaggtcccc	tccatggccc	tgaatcctcc	tctgtctcag	1620
ggctggcctc	tgcaagctg	attaaacagt	gttgtgactg	tctcatggga	agagctgggg	1680
cccagaggga	ccttgagtca	gaaatgttgc	cagaaaaagt	atctcctcca	acaaaaacat	1740
ctcaataaaa	ccatttttagt	tgaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaa	1797

<210> 70

<211> 1373

<212> DNA

<213> Homo sapiens

<400> 70

ggcacgaggg	ctgacggcgc	ttttgtctcc	ggtgagtttt	gtggcgggaa	gcttctgcgc	60
------------	------------	------------	------------	------------	------------	----

tggtgcttag	taaccgactt	tcctccggac	tcctgcacga	cctgctccta	cagccggcga	120
tccactcccc	gctgttcccc	cggagggtcca	gaggcctttc	agaaggagaa	ggcagctctg	180
tttctctgca	gaggagtagg	gtcctttcag	ccatgaagca	tgtgttgaac	ctctacctgt	240
taggtgtggt	actgacccta	ctctccatct	tcgttagagt	gatggagtcc	ctagagggct	300
tactagagag	cccacgcct	gggacctcct	ggaccaccag	aagccaacta	gccaacacag	360
agcccaccaa	gggccttcca	gacctccat	ccagaagcat	gtgataagac	ctccttccat	420
actggccata	ttttggaaca	ctgacctaga	catgtccaga	tgggagtccc	attcctagca	480
gacaagctga	gcaccgttgt	aaccagagaa	ctattactag	gccttgaaaa	acctgtctaa	540
ctggatgctc	attgcctggg	caaggcctgt	ttaggccggg	tgcggtggct	catgcctgta	600
atcctagcac	tttgggaggc	tgatgtgggt	ggatcacctg	aggtcaggag	ttcagaccag	660
cctcgccaac	atggcgaaac	cccattctta	ctaaaaatac	aaaagttagc	tgggtgtggt	720
ggcagaggcc	tgtaatccca	gtccttggg	aggctgaggc	gggagaattg	cttgaacccg	780
gggacggagg	ttgcagttag	ccgagatcgc	actgctgtac	ccagcctggg	ccacagtgcg	840
agactccatc	tcaaaaaaaaa	aagaaaaagaa	aaagcctgtt	taatgcacag	gtgtgagtgg	900
attgcttatg	gctatgagat	aggttgatct	cgccttacc	ccggggtctg	gtgtatgctg	960
tgttttcttc	agcagtatgg	ctctgacatc	tcttagatgt	cccaacttca	gctgttggga	1020
gatggtgata	ttttcaacct	tacttcttaa	acatctgtct	ggggttcctt	tagtcttgaa	1080
tgtcttatgc	tcaattattt	ggtgttgagc	ctctcttcca	caagagctcc	tccatgtttg	1140
gatagcagtt	gaagagtgtg	tgggtgggct	gttgggatga	gatggagtgt	tcagtgccca	1200
tttctcattt	tacattttaa	agtcgttcct	ccaacatagt	gtgtattggt	ctgaaggggg	1260
tgggtgggatg	ccaaagcctg	ctcaagttat	ggacattgtg	gccaccatgt	ggcttaaatg	1320
attttttcta	actaataaag	tgggatatat	atttaaaaaa	aaaaaaaaaa	aaa	1373

<210> 71

<211> 1579

<212> DNA

<213> Homo sapiens

<400> 71

ggcacgagga	tttggagggg	acaaacatcc	aaaccattta	agtcacagca	ctttactccg	60
cagtgtgaat	aacacaggca	ttctcctaca	taatcacagt	acagtatatca	tactctggaa	120
attgaatatc	atctaataa	ctttccatac	ccagattttc	ttagattttc	caatgatatt	180
tcttactgtc	ctccctttag	ccttccctct	tctccattca	ggattctacc	attacatttc	240
attttcatgt	ctcttcagtc	tctcttttag	tttgttttcc	tttcttgatg	ttgccacttt	300
taggagggca	ggccagttgt	tttgtgaaag	atctgttctc	tttgatatgt	ttcattttgg	360
atttgtttca	ttgtttttgc	atgaatggat	tcaggctaaa	catttttggg	caggactgtt	420
tattgtatta	cctagtgtatg	tgttcttttc	agtcacatcat	ctggaggcac	ctgatggcag	480
ttttcccaat	attgcgaaat	taagtttgat	tattttgtta	aggtagtgtc	caccagatct	540
ctccatttta	aagacatcct	tttctctaat	tactcagtgg	actgtagagt	gatgctttga	600
aactgaataa	ctaactctcc	ctaactcagt	gatttagcac	ccgttgattt	tttttttttg	660
cctgaatcaa	atattattat	agtagtttta	aatggtgatt	ttccattttc	attcttttgt	720
tagctgccat	tcttctataa	ttttgtcttt	atattttact	gggtgttaag	attgctattc	780
cagctttcct	ttgtctttta	caccttttcc	cattctttta	tttttttcca	tccctttttg	840
tctgttttcc	caatagatgg	atagaatttt	ctttctctgg	tttaaagggt	atacatttgt	900
gtgtgtgtgt	gtattctaaa	ccatttgccc	ttaaaacata	gagatggtta	ttcctgttga	960
ttaaaaaaaa	ctcagtaatg	ttactatctt	ctctttaata	agataggtag	tttattttcat	1020
tctgtgttct	tgggtgaggt	ctccctccac	ccagtcaagt	tgatgttaat	ctagaatttt	1080
tagtttttta	aattatcgat	atactttctg	tcttttccct	tttttttccac	tctctctgta	1140
tttgtgtctt	ccccctttac	tctctttccc	ttcatttccct	ctttctcact	ttcttcttct	1200
attttttact	cttgggtaga	ttatctttta	gaaaacagca	agatattata	taatttactt	1260
tatattctct	ttccaaatga	ttaaagtaat	aattaaaaat	ttttgatatg	tgtgtatgca	1320
aggataggaa	tcctcttgta	agtgggaagaa	ctctaccaca	tgcagtgtgc	attagtgtgt	1380
taaacactgg	gaagtggctt	taggtccagc	tgggtgctct	gaagaaggta	ggtttcttca	1440
gttctttatg	tttaactgtct	ccttacctta	aaaaaggagt	gaagaatact	gactgcagag	1500
gttttgtgag	gattccggta	acacagaagc	atagaactgg	aaaagaatat	taatatattgc	1560
caaaaaaaaa	aaaaaaaaaa					1579

<210> 72

<211> 1028

<212> DNA

<213> Homo sapiens

<400> 72

gcacgacaat	tgaactgaac	cctaaaaatg	ctacttcaat	tcaccttatg	ggattttggt	60.
gctatacatt	tcccgaatg	ccttggtatc	aaagaagaat	tgctaaaatg	ctgtttgcaa	120
ctgcctccta	gttccaccta	tgagaaggta	gtatgatgtc	ctttgttaag	ttagtagcga	180
tttcttgaac	cacagcgccc	attctaccat	gtgttcaca	cattgtggag	ctctggattc	240
agtgaagggg	acttgaggca	atttccttaa	cgatccaatt	caactgtgtt	atcacaaggc	300
ttaacactta	ttatccttga	ctgggtgagtg	gttttctttt	tccccgttag	gtgagtggct	360
ggtaattctg	gaataactgtc	atctaaaatg	gctcgtggct	aaaatctacc	ttcattttct	420
gtttgaaatc	taaactatat	tgaagtcata	aaatagaaca	agaaatacag	catctgttac	480
ccagcatggt	ttagctgtat	tacacacaat	aacagaaaag	taaagcagat	gcttaagttg	540
ataaaaagag	aacactcatt	ataacttcta	ttttaaaaag	catatgaaag	gttcatattc	600
tctcatattt	tcaaggcctt	ttgcttttct	tgtaaaaaat	aagatttgag	aggaatttct	660
ggttaaactt	tgggtttact	catcacaagc	tttccagagt	aagaaaacag	gcaatcgaaa	720
aagctgtact	tgtattattt	acattataac	aaggagcctt	tttttctttc	tgggaagcta	780
tagtgtagaa	attgatgtaa	aaaatactta	gttgatttct	ttacacacag	ttgagaaata	840
ttattaaaaat	aatgcaccaa	tattttataa	tggattattt	aaaataatgc	ccatttgctg	900
gacacggttg	ctcatgcctg	taatgccagc	attttggaag	gccaagggtg	gtggatcagt	960
tgagcctggg	agtttgagac	cagcctgggc	aacgtggcaa	aacccttgca	aaaaaaaaaa	1020
aaaaaaaaaa						1028

<210> 73

<211> 3674

<212> DNA

<213> Homo sapiens

<400> 73

ggcagagact	caaaagaaat	agggtgattt	ttaaaggatt	aataaaatc	tgaatgtta	60
agtagaagat	tacattgtct	agtcttgtat	ttctccttc	tgttgctctc	tttcattcac	120
acactctcag	tttctcatat	tttagactca	tttatttggt	tatttcctaa	gaatattgaa	180
agtgaaagca	ctatgtgact	gtattcttca	ggtaaacact	gactgcgctt	gttggtttt	240
ccctattttt	gtgacttcaa	gaataaatatg	ccctgctgaa	tacatgccat	ttcacattct	300
gaaactgggt	agagtgggtg	gggtttctgc	caacaattgc	tagtggtgtg	aattcattca	360
tatttgccag	tattgctcac	ttcaaagaaa	ctccttcac	aagcagcca	gagctaggcc	420
agatcaatgc	tacaatcatg	aagtctctcat	tgcatgcaat	tgtgtaggat	tgacaaggaa	480
ctcagataaa	aatttccagg	gtgcacttcc	agaaccagct	tcaacatatg	tctacattgc	540
ccccaggtta	ataaagtgcc	aaccctttac	tctctcatac	agccagaaat	gttagaaatc	600
caaaatcttg	gtgcattatt	ttttcataaa	cgctaaaaca	tttgaagaaa	caatttaatt	660
atttaaaatt	caagtatttt	attcacatta	tttgcaatat	ccaaatgttt	aaaaattccc	720
agataattaa	ctagctatta	cagatctcac	ctagagggtt	gatgttatga	agactccagt	780
ggactgtact	cacaaattga	ctggacaccc	tatgaaagtg	ggtagacctc	tcagcggaaa	840
ataagaaggg	cttttaccta	cagggcagga	cagggctcca	tgagagcagt	tctgtggaga	900
tataaaaaga	atggaagaag	gaatgcctta	tagtgatatt	gtgacattat	atctatatat	960
ctacatatat	ctatctatct	atatctacat	ctatataatc	ttacatttaa	aattgtattc	1020
ctacacatat	tagaaactct	tctaataaat	gaagtaaaaa	aattaaaaag	aatacaaaata	1080
ttccagcccc	aaatgagaaa	tcaaacatat	taaaattgtt	caagaaaatt	tctttgaaca	1140
cttctgaaag	tttttggaag	cttagaaaaag	agggaaaaaa	atccagtgtt	actagtaatt	1200
tccatggtta	tacagataaa	atacattctt	ttaattcttg	gaaattagaa	aaagtggggt	1260
gatctttcca	ggaaaaacat	gtgtaacatc	tgcttatcac	tccagctccc	tcctcctcct	1320
cctctccacg	ttcccttgag	taaatgtctg	ggaaagcatg	aagcttgatg	caagaaccct	1380
gttgtagctg	cgttttcctc	ccctgtgaaa	acgtaactac	tgttgggagt	gaattgagga	1440
tgtagaaagg	tgggtggaacc	aaattgtggt	caatggaaat	aggagaatat	ggttctcact	1500

cttgagaaaa	aaacctaaga	ttagcccagg	tagttgcctg	taacttcagt	ttttctgcct	1560
gggtttgata	tagtttaggg	ttggggtag	attaagatct	aaattacatc	aggacaaaga	1620
gacagactat	taactccaca	gttaattaag	gacgtatgtt	ccatgtttat	ttgttaaagc	1680
agtgtgaata	gccttcaagc	atgtgaataa	tcttccatct	tccccgccac	acatacacac	1740
acacactttt	tgtttctttc	aggtagacac	cttttaaaat	gcagaactaa	ctgaggcatt	1800
tcagtaactt	tgctttcaaa	tcaataaagt	caaatgtatg	gaaacatttt	gtgccctact	1860
ctccataccc	cgtgtactca	aattctctac	tgatgaatt	atgctttaag	tagaattcag	1920
tgccaaggag	aacttggtga	aataaattat	tttaattttt	tttttatcct	ttacaaagcc	1980
atggatttta	tttggttgat	gtgtgctctg	tacacaagcc	atttcaatag	gatggagctg	2040
ttaattattt	tccaaagagt	aatagacatg	caaaagtttc	aataaaaact	gggccattaa	2100
caagtaaatt	aataaactaa	taagcattcc	cttctaggtt	tttgccaaac	tgccatcca	2160
atacaaaatt	tgagaatcgt	tgtaaaagct	agttatatatt	cagagaaatg	attttcatta	2220
ttgaaactgt	tctccctagc	aggccatttt	ccctttttcc	tgggagttta	gcaagttag	2280
gagagaatag	tcatgaaaag	aaagggaga	aaggggagaa	gggaagaggt	taaaaagtaa	2340
gtgctcagac	ctatgaacgt	aatccctttg	ctacaaatat	ttaagagcag	ctcagcttgg	2400
ttgaaactga	gttttgtcat	cttccatatt	tgtaggaagg	tattttctga	cttgcaatgc	2460
agctagatgt	aaaattttat	tttatcatcc	tagaaagcct	tgactagaaa	aatgaataaa	2520
tattgagggt	ttcctgtcca	tatctggctt	gcatgtgcca	gaaagcagag	aatagaaaat	2580
gtaactctca	acatccaagc	atcgaaaccc	aaggggtagg	caattctatg	taggttttgg	2640
acatgaagtt	tggtgcatct	tggtttatgc	tggctcaact	gctattaaac	ctctctggct	2700
tatagtctct	tcattctatt	agacaagcac	gtatcgaaca	cttgcttcgc	acaaggctct	2760
ttagttaaca	atthagcagc	tactgtttgt	gttaaacaca	cttttcacca	aataggttct	2820
gaggcaaacg	agagcaatga	ctatttaaag	aaaggctttc	ccagcatcac	ttacacatcc	2880
caaaactaaa	aagatcaact	cttccaactg	agaaaagact	cctggctttg	aatggaaact	2940
tacagcagag	agtcacaggc	cacggcaaca	acaacgacaa	caacaacat	ttggaatatt	3000
attctcaact	caggttttaa	taatacatct	tattattttt	ctagtagaga	aactacaaat	3060
cagcctcttc	aacatttata	tacagttaa	taagcctctt	gcaagttaact	tgttctctca	3120
cctgagggtat	tttttctctc	cccaccttgc	ccctgttcct	cccttctct	tctcccttgg	3180
caagaggaaa	tatttaacat	atttgggtcc	aacttcaata	atgtaataat	taatacatta	3240
aaagcattta	acttcctttc	tagaaaaatg	cacaggctaa	ggcatagaca	aaacaaagag	3300
aatgctgag	aaatttgcca	ctggagacaa	gcaatctgaa	taaataattg	ccaaaagtcc	3360
tttttatgtc	atatagtgtc	aggatttgaa	ggagctatct	ttttttaatg	ttgcaactag	3420
caactcatct	tgggaagaca	cagccaggag	aatgaagtag	aagtgaagag	tttataaatc	3480
catttgtaag	catttatccc	atatatttta	aattcaagaa	aaattgtgtt	tatctttaga	3540
attttgtatt	caatacttta	tgtactatgt	gactcatgct	tctggataaa	taaagcaca	3600
aatatgtatc	tgtaaccaca	atcacacata	ttatatataa	tatatatcta	tataacaaaa	3660
aaaaaaaaaa	aaaa					3674

<210> 74

<211> 2797

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (853)

<223> n equals a,t,g, or c

<400> 74

ggcacgagag	agcagacaga	attatatgta	gaggacacag	gagatattta	cattgtggat	60
ggagatggag	gattgaataa	cagattgatc	aaactgtccc	aagatttcat	gaccccttgg	120
ctgcatggag	aaaatgggac	agggcctgct	aagtccaaca	tacctcacag	tgttacactt	180
gattcagctg	gtcgggtgtg	ggttgctgac	cgaggaaata	aaagaatcca	agtatttgat	240
aaagacactg	gggagtgtt	aggagcatgg	aataattgtt	tcacagaaga	ggaccttctt	300
cagtcagttt	actcctgatg	ggaagtactt	gattgtggcc	cagctgaatc	ttagcaggct	360
ctcagtcgta	gcagcacccc	cagtggaag	cattggggag	tgttctgtga	tcagcacaat	420
ccaactagca	gatcaagttt	tgccacatct	cctagaagtc	gacagaaaag	actggagcag	480

45

tctatgtagc	agaaattgga	gcaaaacaag	tacaaaaata	tgtccctttg	aatagctatg	540
ttccttcatt	tggttcataa	tgtttctttc	ccgggaatat	ttcaagtggc	agttcagatt	600
ctcaattcac	taagtgccta	aaaatgatgt	tcaagcaca	gaatttattt	ttctagtata	660
aaagatctag	tatcagaaaag	atttgttttt	gtatcattaa	gaatcttata	ttttgttgcc	720
ctcttgggac	ttagttttat	ttgtaagtgc	ataaggatat	tttaaatgaa	ggaaagttaac	780
taaaaaatgg	ggttgggaag	agggactaag	gtggtaacct	cattatttgc	cctggttagac	840
tgattctccc	tgngtaaaaa	aaatgggaat	aaaaatgagc	ttgcatgata	atttattaaa	900
tttcatgtga	agaactccag	acctccagat	tgtgcaacta	acataaagtg	agctgcttga	960
gagattgtaa	ataagatgaa	ctattgatta	atttgagtac	ccacagagtg	ctgtgtcttg	1020
acgacttaaa	aatgaaaaag	catgattgcc	ttttgagtag	cttgagctct	agtggggaga	1080
caagcaggga	aacagtcaca	acacagcaaa	agcgaccttg	gagcatagtg	ggacttttgg	1140
agtaggagtg	ctgcatttga	ctgagggaat	catggatact	tcgcaggaga	agtgaatttg	1200
agctcagact	tgaaaactga	ggaggagctt	accaaggagc	aaggaggaga	aaacaataat	1260
ttccaagtaa	agaagggtata	aaaagttaga	agtgtactgt	aaactttgat	aggcttttag	1320
gcctttttta	aagcccaact	tggcttctgt	ccattaccta	taagatat	aatgtcagtc	1380
agcctttaaa	tgtaggaaata	aaatggctgg	catctaagca	cttttagtaa	agaggttttt	1440
acaaataact	aaggattgta	gagcttcctt	ctcttttttt	ttctttttct	ttcttttgtt	1500
ttacatgaac	tcaacttatt	cctaacattt	gtctacctca	aagaaatttc	aagattattt	1560
agataacatg	gatatgtgcc	aaatcctttg	agctgttaag	atgataattt	cctgctttcc	1620
tcctacatct	tctcctccca	ctccctcctt	tgggtgtaag	attggcttcc	caattaagac	1680
cttttttttt	tccagtttgt	tttagcttat	tataggtttt	ggaggaactt	tgccattttg	1740
taatctttca	aatcattctt	cacccttctt	cacatcagct	tcttgctttt	cccagtggtt	1800
tactgtaaat	tgtgtagcat	atgacaaatc	ttgagctgac	tttctcttct	acctgttatg	1860
gctggagtat	tttccagacc	tgaagggact	cacacttggt	ttgatacttg	gatcacatct	1920
ccgtgaggtt	aggaaggtta	atctaccaac	aggaagccct	gtactctgta	ttccaaggcc	1980
attggtaaat	gtgttggtgc	cactgatcgg	actgtatgac	cttaaacaa	tcaccttagt	2040
tttcagtgaa	atgggaatat	cattgtctcc	tctttcatga	atgctgtgag	aatcagatgt	2100
gcaacaggta	catacttgcc	ctttggaaat	ctaatacctc	tgggatacca	ttaagaggca	2160
ttttaattaa	acaaaagggc	ccttctaaat	gtgctattta	tttgacaata	actatcagat	2220
ttgccttaat	tttgtgttta	tagcatttat	caaaacgtat	cctcatagac	tttatgcaga	2280
ttaatatggt	caattgattt	ggataaaaga	aagtaatttc	agggtttgtt	tttaagccag	2340
gacaagaagt	gcaaatgcct	ctttgaagca	atttaggcta	aactgatttt	gaaatttcaa	2400
aatgttttat	tttactttgt	tttattaagc	caggacaaga	agtgcaaatg	cctctttgaa	2460
gcaattcagg	ctaggtaaac	cgattttgcc	atttcaaaac	gttttatttt	actttgwttt	2520
rtrtcagagt	yttawaarvc	ctgctgcaaa	tatttctgaa	tgtctttgta	aaagtgtttg	2580
ttagtgtacc	tgtgattata	gtacttcact	tttttcttct	ggattaattg	gttaaatgaa	2640
tgagaaatgt	gttatgtttt	ttactaaaaa	gtataaatga	aaattttgga	aagaaaaggc	2700
aatattatct	ggctccccaa	ttaaagtttg	attttattgt	cacaaaaaaa	aaaaaaaaaa	2760
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaa			2797

<210> 75

<211> 2703

<212> DNA

<213> Homo sapiens

<400> 75

ggcacgagat	ttctacagg	tgaacgcc	tcattaggat	tactgtaac	gttagtgcta	60
ttaaactcac	tagcattttt	attaatggcc	gttatctaca	ctaagctata	ctgcaacttg	120
gaaaaagagg	acctctcaga	aaactcaca	tctagcatga	ttaagcatgt	cgcttggtga	180
atcttcacca	attgcatctt	tttctgccct	gtggcgtttt	tttcatttgc	accatttgatc	240
actgcaatct	ctatcagccc	cgaaataatg	aagtctgtta	ctctgatatt	ttttccattg	300
cctgcttgcc	tgaatccagt	cctgtatgtt	ttcttcaacc	caaagttaa	agaagactgg	360
aagtactga	agcgacgtgt	taccaagaaa	agtggatcag	tttcagtttc	catcagtagc	420
caaggtggtt	gtctggaaca	ggatttctac	tacgactgtg	gcattgtactc	acatttgagc	480
ggcaacctga	ctgtttgcga	ctgctgcgaa	tcgtttcttt	taacaaagcc	agtatcatgc	540
aaacacttga	taaaatcaca	cagctgtcct	gcattggcag	tggcttcttg	ccaaagacct	600
gagggtact	ggtccgactg	tggcacacag	tcggccact	ctgattatgc	agatgaagaa	660

46

gattcctttg	tctcagacag	ttctgaccag	gtgcaggcct	gtggacgagc	ctgcttctac	720
cagagtagag	gattcccttt	ggtgcgctat	gcttacaatc	taccaagagt	taaagactga	780
actactgtgt	gtgtaaccgt	ttccccgctc	aacccaaatc	agtgtttata	gagtgaaccc	840
tattctcatc	tttcatctgg	gaagcacttc	tgtaatcact	gcctgggtgc	acttagaaga	900
aggagagggtg	gcagtttatt	tctcaaacca	gtcattttca	aagaacagggt	gcctaaatta	960
taaatgtgtg	aaaaatgcaa	tgtccaagca	atgtatgatc	tgtttgaaac	aaatatatga	1020
cttgaaaagg	atcttaggtg	tagtagagca	atataatgtt	agttttttct	gatccataag	1080
aagcaaattt	atacctatct	gtgtattaag	cacaagataa	agaacagctg	ttaatatttt	1140
ttaaaaatct	attttaaaat	gtgattttct	ataactgaag	aaaatatctt	gctaatttta	1200
cctaattgtt	catccttaat	ctcaggacaa	cttactgcag	ggccaaaaaa	gggactgtcc	1260
cagctagaac	tgtgagagta	tacataggca	tacttttatt	atgttttcac	ttgccatcct	1320
tgacataaga	gaactataaa	ttttgtttaa	gcaatttata	aatctaaaac	ctgaagatgt	1380
ttttaaaaca	atattaacag	ctgttaggtt	aaaaaaatag	ctggacattt	gttttcagtc	1440
attatacatt	gctttgtgtc	aatcagtaat	tttttcttaa	gtgtttgtg	attacactac	1500
tagaaaaaaa	gtaaaaggct	aattgctgtg	tgggtttagt	cgatttggtc	aaactactaa	1560
ctaattgtgg	ggtttaatag	tatctgaggg	atttggtggc	ttcatgtaat	gttctcatta	1620
atgaatactt	cctaataatc	ttggctctac	taatatcttc	caatttgctg	ggatgtcacc	1680
tagcaatagc	ttggattata	tagaaagtaa	actgtgggtc	atacttgcac	ttaattagac	1740
gaaacgggga	gtaattatga	cacgaagtac	ttatgtttat	ttcttagtga	gctggattat	1800
cttgaacctg	tgctattaaa	tggaaatttc	catacatctt	ccccatacta	ttttttataa	1860
aagagcctat	tcaatagctc	agagggtgaa	ctctgggttaa	acaagataat	atgtttattaa	1920
taaaaataga	agaagaaaga	ataaagctta	gtcctgtgtc	tttaaaaatt	aaaaatttta	1980
cttgattccc	atctatgggc	tttagaccta	ttactgggtg	gagtcctaaa	gttataattg	2040
ttcaatatgt	tttttgaaca	gtgtgctaaa	tcaatagcaa	acccactgcc	atattagtta	2100
ttctgaatat	actaaaaaaa	tccagctaga	ttgcagttta	ataattaaac	tgtacatact	2160
gtgcatataa	tgaattttta	tcttatgtaa	attattttta	gaacacaagt	tgggaaatgt	2220
ggcttctgtt	catttcgttt	aattaaagct	acctcctaaa	ctatagtggc	tgccagtagc	2280
agactgttaa	attgtggttt	atatactttt	tgcatgttaa	atagtctttg	ttgtacattg	2340
tcagtgtaat	aaaaacagaa	tctttgtata	tcaaaatcat	gtagtgttga	taaaatgtgg	2400
gaaggattta	tttacagtgt	gttgtaattt	tgtaaggcca	actatttaca	agttttaaaa	2460
attgctatca	tgtatattta	cacatctgat	aaatattaaa	tcataacttg	gtaagaaact	2520
cctaattaaa	agggtttttc	caaaattcag	gttattgaaa	atttttcatt	ttattcattt	2580
aaaaactaga	ataacagata	tataaaagtg	ttaatctttg	tgctatatgg	tatgaaatac	2640
aatatgttac	tcagtgtttt	gaattattaa	agtttctaga	aagcaaaaaa	aaaaaaaaaa	2700
aaa						2703

<210> 76

<211> 742

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (707)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (724)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (726)

<223> n equals a,t,g, or c

<400> 76

47

gcgctcgaga	atagtgggtc	ccccggrctg	caggattcgg	cacgagctca	cttcaatyct	60
tctttgagaa	gtttttcctt	tctccgcaac	cagatgtaca	tatttgaact	ctctttgtac	120
ttggagggca	cttctttcgt	ggtagtctct	ttatttttat	taatctctgt	atccttagat	180
agtccctcaa	caaccaaagg	ttgggactct	gtccttacata	tctgggtgcc	cctcatagtg	240
cagtaataag	taagttgatt	atatacgagc	tatgtaactt	atatttttta	atgggtggat	300
atcactgagt	tttttttttt	aagaattttt	ttattgaggt	aaacttcaca	taacataaaa	360
ttactatttt	taaagtgaga	agttcagtcg	cacttagtat	tgtaacaat	gttgcataac	420
caccaccttt	atttaaagtt	ccaaaaaaa	tgtctcctc	taaaaggaaa	ccccatccca	480
ttaagcagat	actctccatt	ccttccttcc	tccagcccc	agcaaccacc	aatctgcttt	540
ctgtctctat	ggatttatct	attcttgcta	ttttatataa	atcgaattgt	atgagacctt	600
ttgtgtctgg	cttctttcac	ttagtacaag	tttttgagat	ttatttacat	agtagcatgt	660
atcaacactt	catttttatg	gccaaataaa	attgtattat	gtgttntag	cacaaaaaaa	720
aaananaaaa	atgaccctcg	ag				742

<210> 77
 <211> 1825
 <212> DNA
 <213> Homo sapiens

ggcacgagca	tgctacatgt	atacctatgt	aacacacctg	cacattctgc	acatgtatcc	60
cagaacttaa	attataataa	taaaaaaaga	ataattgggt	gatggcacat	ccagggttgc	120
caaagacagt	cccagtttat	gctgttgctc	tggcattatt	aataatgaca	ctgcctttaa	180
ctctcacaat	taatttggat	gataacttat	atggaactc	tgctaaataa	aaaaaataaa	240
aattaccata	gtaacaggaa	cctacttgaa	atgatgcctc	tgtttctatt	ctggcttgaa	300
ttctgcattc	tttgaggatt	tgtagcctca	tgacagaatc	ctatctacag	gtgatgtatt	360
tcatatgatt	tttggtctatt	tttttaacaa	tctcaagccc	aataatagcc	agtgatataa	420
ggaatgtagt	tactttctcc	ccactttctg	gcaagttaag	tttagccacc	tgattacaag	480
aagggacatt	cagaggtagg	atggcacaaa	gacacaggtg	ccactggaga	tcactggaag	540
cagctgcagc	agggttaaga	gaagggagtc	ccagcgagtc	ttcagtcacc	acacactaac	600
atcatcagtg	aaaagtccct	gggcctgaag	atccagctat	gttggttcta	gttgactatt	660
ttaagtgaca	gaacttggcc	caagcattga	ccattttggt	tcctcaataa	gcctgattca	720
accaggggtca	ccttttgaatc	tgctctccac	ctttccaata	aacctatttt	atgcatcatt	780
cagtgaagtta	tttattttatt	tacttttttg	ctgagaaaca	tgactagatt	taggaaaaat	840
gtagaatttt	actttttttt	caatattttc	tgggttttcc	agagttttca	cgtgtttcac	900
gccttccctt	gcttcccacc	attccccttt	ctatttggaa	ctagagagac	atgagtttga	960
attctagctg	tgtaacctga	gtcagttatt	taacctcttt	ttgtttctgt	ttctttgtct	1020
gtaaatagca	aaaactacaa	ttaacttttag	tccctgctgt	acaccaaagt	ttatcttgaa	1080
atattataca	tattatatgt	aattactact	gaaatgctct	aagatgccta	tgtgtgaatg	1140
gcatttggtg	aaagattaaa	taatataagg	gaagtgtctg	cttcagtgtc	tgcatataaa	1200
taaaagctat	tattttttacg	attattttcc	atcttataga	agaattatcg	ttcttccctt	1260
ccaaagctaa	taaatggaca	tgtgtttatc	agacagaacg	taagagctgc	caaataaata	1320
gggaataggt	gctttcggga	gtctagggaa	ataaagggtca	gggaattggt	cataaaaattt	1380
agtaccata	aatagcctat	aagtagattc	cctagtttat	tctatgcagg	aaaaataaagt	1440
tctacggagc	acagattcca	aaactaattg	gtcataaata	tcacctgaaa	gtttagaaaa	1500
tgtagcatca	tggacctctt	ttcataggtt	ctaaatctta	atatctgtgg	gatgggtgcag	1560
gaatctagct	ttgctaagtg	ccctcagatg	actcttgctg	ttctaggcta	aaatacatgt	1620
ggtttggctt	caatggacat	gttcctgaag	aatgtttgga	tgctcacacat	tcataatttag	1680
tatgagagat	gaggtcctcc	tctcatcatt	ttcttaggtt	ctcttctctc	cactccttac	1740
cctcccatca	cttacaataa	atcttttaga	aaattagcta	tacatttggt	tcattataaa	1800
aaagaaagaa	gataaaaaaa	aaaaa				1825

<210> 78
 <211> 1674
 <212> DNA
 <213> Homo sapiens

<400> 78
 ggccacgaga gtatctgcgg cagctgcagg tcctggattt atttctcgat tcgctgtcgg 60
 aggagaatga gacctgggtg gagtttgcta ttggaggcct gtgcaacctg tgcccagaca 120
 gggccaacaa ggagcacatc ctgcacgcag gaggtgtccc actcatcatc aactgcctat 180
 ccagcccaaa tgaggagacg gtgctgtctg ccatcaccac gctcatgcac ctgagcccg 240
 cgggcccag ctttctccca gagctgaccg ccacgcccgt ggtgcagtgc atgcttcgct 300
 tctccctctc ggccagcgcc aggttccgga acctggcaca gatcttcctg gaggacttct 360
 gctccccccg ccaagtggcc gagggccgca gccggcaggc gcaattttgc cctgggtatc 420
 ccactgccga ggagcgtggc cccacggcag cgctgatcca tggagactgc gagaccgtgg 480
 caccctact gctggggacc acagtcctga tgtggacgca gggaaacggg agcacatact 540
 gccccattgg tgccttttca gccatctgaa aggcgggttc tttcagcagg acaggcattt 600
 aactgatga aacgccactg ggagtggga agccagactc cagagacacg gagaagatca 660
 aactggagct gcgttcatag gctggcactc tcaatcctac atcaggtgcc accaccacca 720
 gactcaggcc ctggtgtaag aagcgcccaa gtgcctggac ccagaggcct tgcaggacag 780
 tgttctcagg agctgggcct gaggcttagg agagctgcct tcgctgcagg aaatcaggga 840
 ttatccctta acagaagtgt ctggagtagt tttcaggtat aggaatgaga tgcctcgtgg 900
 tgaaagatc tcaccctggg aagatgtggt gccccctcca gggctctgga ggatggatgc 960
 ctccccagg ggtctctcaa gctgggcatt tgggcctggt ggatgccaac ctggataacc 1020
 tgtggcccag cattgactgt ccaccagcc ttgctgttag gcaccatgac tccaaagatg 1080
 aagatgtggt ccctgccctt gactgacagc ccaggggact taatgtggcc atcgggcatc 1140
 aagcacaaag ccatgcaggt gatgatacgt cggaatagag gcaccagccc tggtactgc 1200
 atcttctccc cttgccaccc catggccccg gctgaaagct tcggccctcc tctgctgtca 1260
 ctcaatgatg gggagcccta cccagaagt gtatcccacg agggcatcag ggacgcagtg 1320
 agtggtgctc aaggagtgca ggaagagacg gcaacgtaaa ggatgtggct ccatgtccat 1380
 ggtgccccct ggtcaacata aggagcgtgg gatccgatgg aaaggtggag ctcagggaaa 1440
 atgggggtcc ttgctctctg tgtacccct caaggctgac cccttagatg gccagggaat 1500
 ggcaggtgct acaaaaatgg taccacgtg ggcattgaaa tggggcagat taggggacca 1560
 ctggactcag aggggaggga agggctcatc agcaccgct caggggagcct gtccctttat 1620
 gttcccaaat aaagggtcct agaagactaa aaaaaaaaaa aaaaaaaaaa aaaa 1674

<210> 79
 <211> 2191
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1327)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1334)
 <223> n equals a,t,g, or c

<400> 79
 ctttctctaa aaaagcaaac aggcaaaact tcatgagaat cttgatcatg ttaaaatttt 60
 atgtccttcg atttctccct acacacacac acacacacac acacacacac acacacacac 120
 tcaacatttc ctccacccat atcatcactc cttagcatct ttattccatc aaaactttct 180
 accccttgac atttctctgt cagttttgaa aattaccctc tcagcattct ctgttcaccc 240
 ccacacctag accctgacct ctagtcaatt ctactacca ggggtgtcca cggttccagc 300
 ctctccatg aagcccagtt ctatgggctc actcctctgg gtaagtggga gccccagct 360
 atcactctca ttgtatagaa aaccaactct gtgatgctac ctgcccctct tccccttctc 420
 tcctgaaaga gggctggggt agaggtggga ggactgggta tggccctggc cgggtctgta 480
 ttcgtactgg gaggagtatt ggtactctgt gtgaaagaa atggggaggg ggaaatgggg 540
 tggcctcagc atctccctaa gtcccagcct ttaagtcctc ctgttcgagt tcgtcgctgc 600

agcttcgaga	ggagttggat	cgatcttctt	gtggaaacgt	cctcttcaat	ggttacctgc	660
cgccaacagg	taggcactcc	caatggaatg	gaggggcgcg	gaggtgggccc	aaagactaca	720
tttcccataa	ggctgcagct	ctcgggtgcc	tgtgctgtgc	gtcctgagat	acagtgggaa	780
gtgtagtccc	ctatcagatg	cttgggctga	tgcttggaaa	ggaagttgga	cacagcattt	840
ccccgaaac	aatgggccc	ctaactcttg	aaagctcaaaa	agatgtcctt	ggaaccccat	900
ggggaatttg	ttatcccggg	tttgggtttc	ttttgttagg	gggggctttg	ggaaaaactg	960
gggattcctc	cgtatggaag	gggaaaaaat	attaaatagg	aagttattga	cattaatgcc	1020
catgatagcc	acccactgg	gccatggaag	gtatgcccc	gtgggtattg	gaactaggct	1080
tttctgattg	gtagaagtaa	cagagtaggg	aaatttcata	tacagcttta	tttccctaac	1140
tgcagtcagc	acctgtacct	tcatgaaagt	tgccagatat	aaagatctgt	agtagtactt	1200
ttccaactta	gttttatcct	gttttcccga	aaaacaatca	tttatttatt	tatttattta	1260
tttaatttta	tgagacaggg	tctggctttg	tcaccaggc	tggagtgcag	tgggtgcgac	1320
ttggctncac	tgcnacctct	gcctctcaga	ttcaagccat	ccttccacct	cagctctgcc	1380
actgagtagc	tgagactaca	agcactcgcc	accatgcccc	gctaattaaa	aaaataataa	1440
tcattttaaa	tgcaagcttt	atattataaa	tacaaagtaa	acatgaaaat	aaaacccaaa	1500
catagcagtg	ttattaaact	ctggcctgta	gcagtggctc	acacctgtaa	tcctagcagt	1560
ttggaggccg	agacaggtgg	attacttgag	acctggagtt	tgagaccagc	ccagggtgac	1620
cagcaagacc	tcactctctac	taaaaataaa	aaaaaattag	ccaggtgtgg	tggtatgcac	1680
ctgtggtccc	agctacttag	gatgctggag	tgcgaggatc	gcttgagccc	aggagggtcaa	1740
ggctgcagtg	aactatgatc	actcattaca	ccccagcctg	ggtgacagag	cgagatgctg	1800
tctcaaaaca	aaacaaaacg	aaaaacaact	ctggctagat	gctattgctt	gccaagggtg	1860
cagtcttcca	tttattaaaa	gtgaaaatta	gggccaggca	cattggctca	tgcttgaat	1920
cccagcactt	tgggaggctg	aggtgggtgg	atcacctgag	gtcaggagtt	cgagaccagc	1980
ctggccaaca	tggtgaaacc	ttatctctgc	caaaaatata	aaagattagc	catgtgtcgt	2040
ggtgggtgct	tgtaatctca	gctacttggg	aggctgaggc	aggagaatca	cttgaaccca	2100
ggaggcagag	gttgagtgga	gccaaagattg	tgccattgca	ctccagcctg	tgcaacgagc	2160
gaaactccaa	ctcaaaaaaa	aaaaaaaaaa	a			2191

<210> 80

<211> 1335

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1287)

<223> n equals a,t,g, or c

<400> 80

ggatatatcc	agggctgcgg	attttccccc	cttcagggtt	aaatgttcct	gtttttctac	60
ctttccctcg	cagtatacgc	tcaacggcaa	gawagtggaa	gttgccgtca	aacagatcat	120
cgctggaaaa	gccgtggagc	aaggaggtgc	tttctcgaa	cccagagacc	tgatctgtga	180
ccgggacatc	cctgagctgc	agggcttctg	agtcagactg	gctggcgtgt	cactcagccg	240
caccogtgtg	cactgtaact	tttgtgtgct	caagaaatta	tacagaaacc	tacagctggt	300
gtaaaaggat	gctcgcacca	agtgttctgt	aggcttgggg	agggatcggt	tctctgtttt	360
gttaaatctg	gtgggtacct	ggatcttcca	cacgagtggg	attctggcct	tcagagacca	420
ggagggagtg	tctgggccc	agtgtggcac	tgtgtgtgaga	gtgtgtgtct	ttgcacacac	480
agtgcagcgg	gaacgggtgg	gctggctggg	gctgaagaca	gacacactcc	tgagccaagg	540
tcttgtcttc	aacctcccc	tcccggtgtc	ccattttgct	ctgtgaagg	gcaaatccct	600
ttcttccctt	cccatctcag	gctctctctg	tttccctcag	ggtccagtat	gcctttgagc	660
tttagctgtt	agaaaggga	ccccgtgact	tgacacagct	ttcacagctg	gctgctagga	720
ccggcgggct	gggtgttcac	gtgtgtctgt	gtcatggatg	caatgcaggc	cctggaggac	780
tgtgcgtcac	ccgtcaacca	gagcgtgcct	ccgggcccagc	ttccctccaa	ggaatgagtg	840
gatttcatac	aggatctctt	tattgcacag	actgaatggc	tttacatgtt	tctaagtga	900
attaggcatg	tgaagcagtg	ggtgtccacc	cgtgtccctc	atgggtgagc	cctccagctg	960
tgagcccagg	cagtgtggtc	accgagtgag	gaccctcctc	accaggaacc	gcacccctgt	1020
gctgcctcca	cctgagagtt	gctaggggtg	tcttgtcgag	atcatgtcat	cagcaccctt	1080

50

aagtcaagtc	acggggtttcc	atagccaggc	agttgggtatg	tacaattcag	ttcagcgtat	1140
gaacttgat	ctctaattctg	atgtccattt	ttatatTTTT	tgaaactgag	cacaatgaaa	1200
tcctttcttg	aatcattttc	cttttggtat	ataaaaaatat	gggggaaagt	gctatgatga	1260
attttatgca	ataaatgtat	acatgtntgc	acatgcaccc	atgctgaaaa	aaaaaaaaaa	1320
aaaaaaaaaa	aaaaa					1335

<210> 81
 <211> 1867
 <212> DNA
 <213> Homo sapiens

<400> 81

cccacgcgtc	cggggccacag	cagagacagt	ggagggcagt	ggagaggacc	gcgctgtcct	60
gctgtcacca	agagctggag	acaccatctc	ccaccgagag	tcatggcccc	attggccctg	120
-----cacctcctcg	tcctcgtccc	catcctcctc	agcctgggtg	cctcccagga	ctggaaggct	180
gaacgcagcc	aagaccctt	cgagaaatgc	atgcaggatc	ctgactatga	gcagctgctc	240
aagtggtga	cctgggggct	caatcggacc	ctgaagcccc	agaggggtgat	tgtggttggc	300
gctggtgttg	cggggctggt	ggccgccaag	gtgtcagcg	atgctggaca	caaggtcacc	360
atcctggagg	cagataacag	gatcgggggc	cgcattctca	cctaccggga	ccagaacacg	420
ggctggattg	gggagctggg	agccatgcgc	atgcccagct	ctcacaggat	cctccacaag	480
ctctgccagg	gcctggggct	caacctgacc	aagttcacc	agtacgacaa	gaacacgtgg	540
acggaggtgc	acgaagtga	gctgcgcaac	tatgtggtg	agaaggtgcc	cgagaagctg	600
ggctacgcct	tgcgtcccca	ggaaaagggc	cactcgcccc	aagacatcta	ccagatggct	660
ctcaaccagg	ccctcaaaga	cctcaaggca	ctgggctgca	gaaaggcgat	gaagaagttt	720
gaaaggcaca	cgctcttgga	atatcttctc	ggggagggga	acctgagccg	gccggccgtg	780
cagcttcttg	gagacgtgat	gtccgaggat	ggcttcttct	atctcagctt	cgcgaggcc	840
ctccgggccc	acagctgcct	cagcgacaga	ctccagtaca	gccgcatcgt	gggtggctgg	900
gacctgctgc	cgcgcgcgct	gctgagctcg	ctgtccgggc	ttgtgctgtt	gaacgcgccc	960
gtggtggcga	tgaccacagg	accgcacgat	gtgcacgtgc	agatcgagac	ctctcccccg	1020
gcgcggaatc	tgaagggtgct	gaaggccgac	gtggtgctgc	tgacggcgag	cggaccggcg	1080
gtgaagcgca	tcaccttctc	gccgcccgtg	ccccgccaca	tgaggaggcg	gctgcggagg	1140
ctgcactacg	tgccggccac	caaggtgttc	ctaagcttcc	gcaggccctt	ctggcgcgag	1200
gagcacattg	aaggcggcca	ctcaaacacc	gatcgcccgt	cgcgcatgat	tttctacctg	1260
ccgccgcgcg	agggcgcgct	gctgctggcc	tcgtacacgt	ggtcggacgc	ggcggcagcg	1320
ttcgccggct	tgagccggga	agaggcggtg	cgcttggcgc	tcgacgacgt	ggcggcattg	1380
cacgggcctg	tcgtgcgcca	gctctgggac	ggcaccggcg	tcgtcaagcg	ttgggcggag	1440
gaccagcaca	gccagggtgg	ctttgtggta	cagccgcccg	cgctctggca	aaccgaaaag	1500
gatgactgga	cggtccctta	tggccgcac	tactttgccc	gcgagcacac	cgcctacctg	1560
cacggctggg	tggagacggc	ggtcaagttg	ctgcgcgccc	ccatcaagat	caacagccgg	1620
aaggggcctg	catcggacac	ggccagcccc	gaggggcacg	catctgacat	ggaggggcag	1680
gggcatgtgc	atggggtggc	cagcagcccc	tcgcatgacc	tggcaaagga	agaaggcagc	1740
caccctccag	tccaaggcca	gttatctctc	caaaacacga	cccacacgag	gacctcgcat	1800
taaagtattt	tcggaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1860
aaaaaaa						1867

<210> 82
 <211> 984
 <212> DNA
 <213> Homo sapiens

<400> 82

gaattcggca	cgagcccagc	ggaagccaag	ccaccaggcc	ccccagcgtc	cacgcggagc	60
atgaacattg	aggatggcgc	gtgcccgcgg	ctcccgtg	cccccgctgc	cgcccggtag	120
gatgtccttg	ccccacgggg	cattgctctt	cctctggctc	ttctccccac	ccctgggggc	180
cgggtggagg	ggagtgccg	tgacgtctgc	cgcggagg	ggctccccgc	cggccacctc	240
ctgccccgtg	gcctgctcct	gcagcaacca	ggccagccgg	gtgatctgca	cacggagaga	300

51

mctggccgag	gtcccagcca	gcatcccggg	caacacgcgg	tacctgaacc	tgcaagagaa	360
cggcatccag	gtgatccgga	cggacacgtt	caagcacctg	cggcacctgg	agattctgca	420
gctgagcaag	aacctggtgc	gcaagatcga	ggtggggcgc	ttcaacgggc	tgcccagcct	480
caacacgctg	gagctttttg	acaaccggct	gaccacgggtg	cccacgcagg	ccttcgagta	540
cctgtccaag	ctgcgggagc	tctggctgcy	gaacaacccc	atcgagagca	tcccctccta	600
cgcttcaac	cgctgcccct	cgctgcccgc	cctggacctg	ggcgagctca	agcggctgga	660
atacatctcg	gaggcggcct	tcgargggct	ggtcaacctg	cgctacctca	acctgggcat	720
gtgcaacctc	aaggacatcc	ccaactgacg	gccctggtgc	gcctggagga	gctggagctg	780
tcgggcaacc	ggctggacct	gatccgcccc	ggctccttcc	aggggtctcac	cagcctgcgc	840
aagctgtggc	tcatgcacgc	ccaggtagcc	accatcgagc	gcaacgcctt	cgacgacctc	900
aagtcgctgg	aggagctcaa	cctgtcccac	aacaacctga	tgctcgctg	ccacgacctc	960
ttcacgcccc	tgcaccgcct	cgta				984

<210> 83

<211> 2664

<212> DNA

<213> Homo sapiens

<400> 83

ggttgtggc	ccaggtagagc	ggcgcgctg	gtccagggtga	gcggggcgct	ccccgcgagc	60
gcgctgcctg	cccagggcgg	ttcacgtaaa	gacagcgaga	tcctgagggc	cagccgggaa	120
ggaggcgctg	atatggagct	ggctgctgcc	aagtccgggg	cccgcggcgc	tgccctagcgc	180
gtcctgggga	ctctgtgggg	acgcgccccg	cgccgcggct	cggggaccgc	tagagcccgg	240
cgctgcgcgc	atggccctgc	tctcgcccc	cgcgctcacc	ctcctgctcc	tcctcatggc	300
cgctgtgtgc	aggtgccagg	agcaggccca	gaccaccgac	tgagagacca	ccctgaagac	360
catccggaac	ggcggtcata	agatagacac	gtacctgaac	gccgccttgg	acctcctggg	420
aggcgaggac	ggtctctgcc	agtataaatg	catgacggat	ctaagccttt	cccacgttat	480
gggtataaac	cctccccacc	gaatggatgt	ggctctccac	tgtttggtgt	tcatcttaac	540
attggtatcc	cttccctgac	aaagtgttgc	aaccaacacg	acaggtgcta	tgaracctgt	600
ggcaaaaagca	agaatgactg	tgatgaagaa	ttccagtatt	gcctctccaa	gatctgccga	660
gatgtacaga	aaacactagg	actaactcag	catgttcagg	catgtgaaac	aacagtggag	720
ctcttgtttg	acagtgttat	acatttaggt	tgtaaaccat	atctggacag	ccaacgagcc	780
gcatgcagg	gtcattatga	agaaaaaact	gatcttttaa	ggagatgccg	acagctagt	840
acagatgaag	atggaagaac	ataacctttg	acaaataact	aatgttttta	caacataaaa	900
ctgtcttatt	tttgtgaaag	gattattttg	agaccttaaa	ataatttata	tcttgatggt	960
aaaacctcaa	agcaaaaaaa	gtgagggaga	tagtgagggg	agggcacgct	tgtcttctca	1020
ggtatcttcc	ccagcattgc	tcccttactt	agtatgccaa	atgtcttgac	caatatcaaa	1080
aacaagtgt	tgtttagcgg	agaattttga	aaagaggaat	atataactca	attttcacaa	1140
ccacatttac	caaaaaaaga	gatcaaatat	aaaattcatc	ataatgtctg	ttcaacatta	1200
tcttattttg	aaaatgggga	aattatcact	tacaagtatt	tgtttactat	gaaattttta	1260
atacacattt	atgcctagaa	ggaacggact	ttttttttct	attttaatta	cacataatat	1320
gtaattaaag	tacaacataa	tatgttggtt	ctctgtagcc	cgttgagcat	atgagtaagt	1380
cacatttcta	ttaggactac	ttmcaaggac	aaggtttcca	tttttccagt	tgtaaaattg	1440
gaaccatcag	ctgataacct	cgtagggagc	aacccagga	tagctaagtg	ttatgtaata	1500
tgccatagaag	gtgatgtgaa	tgcgattcag	aagcatagcc	actcccattt	tatgagctac	1560
tcacatgaca	aatgtcatct	tttgctataa	cctttgccaa	gtagagaaa	agatggattt	1620
aatgagataa	atgaaaagat	atttamccta	atatatcaag	gcactatttg	ctgttatgct	1680
ttgttattta	tttcccagca	cttgttcctt	attgtagatt	ttttaagac	tgtaaccttt	1740
tactaactgt	ggtcttacta	aaatttgtgc	ttgatactgc	ttttcaaaaa	gcctttaatt	1800
agagccaaaa	ggatggaaaa	ggcaagatat	aaatgccttt	tatagatctc	ttatttacat	1860
tgaaaattat	taccatatgt	ttagagcaaa	tccaagaaaa	cttcaacagc	ttctgaagat	1920
gtctatgaat	gttgaaaact	tttcaatctc	ttggaatgct	cagttatggt	cctagaccgg	1980
tctttgtctg	ctactgggtg	ttaacctttc	cctagcctgg	gacctcaagc	catatatatc	2040
ctttgggtga	cccatggcca	aagttattaa	gatgaactga	ctttcaaagt	cagagaagga	2100
cagcataggg	agaggcggtt	atttgtaagt	cattacaggt	agaacagggc	agaaggaaaa	2160
gtatgttctg	gagaaagggc	catgttccta	actttggaga	tatgtcattg	ccgggaacct	2220
agtatcttcc	aacttgaatt	ggtggcagct	gttccagtg	gacaaggcac	atgtatgcct	2280

52

tgtgggctaag	tgagcaaact	gggtttccac	ttaaagtgtt	gggaccctca	attgattctt	2340
tatttcaaac	ctttataaaa	ggtacagttt	tgtaagccat	tattaataat	taatgcttat	2400
cggctgggca	cagtggctca	cacctataat	cccagcactt	gggaggctga	ggcgggtgga	2460
tcacttgagg	tcaggagttt	gagaccagct	ggccaacatg	gtgaaacagc	gtctctacta	2520
aaaatacaaa	aatttgccgg	gcgtgggtgg	gcatgcttat	agtctcagct	actcaggaag	2580
ctgagggtacg	agaatcactt	gaaccagga	ggtggagggt	gcagtgagct	gagattgtgc	2640
cactgcactg	cagcctggct	cagag				2664

<210> 84
 <211> 1328
 <212> DNA
 <213> Homo sapiens

<400> 84

cccacgcgtc	cgggccagtg	gaggtccgca	gagtttgggc	gccaggcgag	acggcagggc	60
ttaaagttcc	gggaatcaaa	gatcaactcc	cactgaggac	aaatggacct	gtaattccgg	120
gtgtgacgag	agaacgagat	ttaccttcct	gaattaaaaa	wcwgactccc	tcgacaagg	180
actgtgtact	gcatgaatga	ggctgagata	gttgatgttg	ctctgggaat	cctgattgag	240
agccgcaaac	aggaaaaggc	ctgcgagcag	cgggccctgg	cgggggctga	taaccagar	300
cactccccctc	cctgctccgt	gtcgcctcac	acaagtctcg	ggagcagcag	tgaggaagag	360
gacagtggga	aacaggcact	grctccaggc	ctcagccctt	cccagaggcc	gggggggttc	420
agctctgcct	gtagcaggag	ccctgaggag	gaggaggaag	aggatgtgct	gaaatacgtc	480
cgggagatct	ttttcagcta	gggcataaac	tgtgactga	actgtctgcc	gagagcagct	540
ggaggacagc	tgagcttcca	ctggtgctgc	tgggccgccc	gcctgtggga	atggggctct	600
ctgtgctcct	acctttgtgc	cttcttgggc	ctggcagatt	cacctcaggc	cagaagcccc	660
tggacactcc	gggccttggg	gctgccgttc	tgagtgtgcg	gaaggcagga	ctcaaatga	720
gateccattt	gactccctct	gtatgtactg	tgccctctcc	tggctcttga	ggctctggag	780
tcccaattgt	ctgtgttagt	cagtgaccag	gttccaggga	aaatgatgtc	atgtggtggt	840
ccaacttact	ggaaccaaag	agacagtact	ttgcaaaaga	aaggatcact	gccaggtgca	900
ctggaattgc	tacagttagt	tccgcatgat	ctctctctga	ggaggaagcc	tgtttcaaaa	960
atagtttcca	tcatgagtct	atcaatgagc	tcccacctct	ccagccagcc	tagaaagcaa	1020
acgagctgcc	cacagtcttc	tgccctgtct	gggaggttga	ggccacagtg	tatagactgg	1080
taagccagac	aggcctcctc	ccgcaagctg	ctacctgtct	ttcacctgta	ccttggtccc	1140
cgggcagcta	gctataaagc	aagagggaca	ggagcccaga	agagacactg	aggacaagag	1200
atcacaccag	agtacatgtc	tctgcctctg	ttttcagtgt	ggctttggac	aggaatatat	1260
gaataaatca	ctgccataca	ggttttccaa	tacacaagtg	ctagaaaata	cacacaattc	1320
cccaatga						1328

<210> 85
 <211> 1342
 <212> DNA
 <213> Homo sapiens

<400> 85

ggccccccca	ggagggtattc	tgcctttgac	tgcaactctt	gtcgtcttat	gtgggtgttg	60
aattgatctg	tctctgcagc	cagatccagg	ctcctggaag	aaccatgtcc	ggcagctact	120
ggtcatgcca	ggcacacact	gctgcccaag	aggagctgct	gtttgaatta	tctgtgaatg	180
ttgggaagag	gaatgccaga	gctgccggct	gaaaattacc	caaccaagag	aaatctgcag	240
gatggacttt	ctggctcctct	tcttgttcta	cctggcttcg	gtgctgatgg	gtcttgttct	300
tatctgcgtc	tgctcgaaaa	cccatagctt	gaaaggcctg	gccaggggag	gagcacagat	360
atcttctctg	ataattccag	aatgtcttca	gagagccrtg	catggattgc	ttcattacct	420
tttccatacg	agaaaccaca	ccttcattgt	cctgcacctg	gtcttgcaag	ggatggttta	480
tactgagtac	acctggggaa	gtatttggct	actgtcagga	gctggagtgt	tccttgcatt	540
accttcttct	gccctatctg	ctgctagggt	taaacctgtt	ttttttcacc	ctgacttgtg	600
gaaccaatcc	tggcattata	acaaaagcaa	atgaattatt	atttcttcat	gtttatgaat	660
ttgatgaagt	gatgtttcca	aagaacgtga	ggtgctctac	ttgtgattta	aggaaaccag	720

53

ctcgatccaa	gcactgcagt	gtgtgtaact	gggtgtgtgca	ccgttttcgac	catcactgtg	780
tttgggtgaa	caactgcata	ggggcctgga	acatcaggta	cttcctcctc	tacgtcttga	840
ccttgacggc	ctcggctgcc	accgtcgcca	ttgtgagcac	cacttttctg	gtccacttgg	900
tggtgatgtc	agattttatac	caggagactt	acatcgatga	ccttggacac	ctccatgtta	960
tggacacggg	ctttcttatt	cagtacctgt	tcctgacttt	tccacggatt	gtcttcatgc	1020
tgggctttgt	cgtgggtctg	agcttcctcc	tgggtggcta	cctgttgttt	gtcctgtatc	1080
tggcgccac	caaccagact	actaacgagt	ggtagagagg	tgactggggc	tgggtgccagc	1140
gttgtccct	tgtggcctgg	cctccgtcag	cagagcccca	agtcaccagg	aacattcact	1200
cccatgggct	tcggagcaac	cttcaagaga	tctttctacc	tgcttttcca	tgatcatgaga	1260
ggaagaaaca	agaatgacaa	gtgtatgact	gcctttgagc	tgtagttccc	gtttattttac	1320
acatgtggat	cctcgttttc	ca				1342

<210> 86
<211> 1154
<212> DNA
<213> Homo sapiens

aagacaggaa	aagctccagg	ccgtggttct	caaagtgtgg	tccttggaca	gcagcaacat	60
cacctaggag	cctgttaggg	aaggcacagc	ctcaggccct	gccccagacc	tgcagaatca	120
gaaactctgg	ggtgaggcct	ggttatctgc	tgtaacagac	cttccagtgg	gttctgatgc	180
cctctagagc	aggagaacca	ctagcttaga	ggttgcagta	tgtttggcat	cttgccattt	240
gtgttagttc	agaggaatgg	ctgaccccca	tgtctcattt	ctaagcttca	ggcagctttt	300
ctcctgggca	gctgtcattc	tgttgagggg	aatcctgggg	actgtggctc	ctcctccctg	360
tcctgtgtgc	cttgatctgg	cagtctacc	ccttcattct	cccgtggagg	ctccatgcct	420
agagggtggt	ttcaaacaga	agaatggcaa	agataattgt	ctcgtgtttt	accctgaccc	480
cattccttta	agagggtcac	ttcttggccc	attcatttaa	aaaccaatgt	catagttctg	540
tgattccacc	tatcagacag	tgccacgtcc	aaaggcgggg	ctctyacctc	cctgggaaga	600
gagactgttg	ctgtctgtgc	ttcctgtgtt	ctccagtccc	acgctccac	ggacccacgc	660
ccttggagac	tcctctrgtg	tcacagggct	tctgggtgtg	tcagagacct	ccacactcaa	720
cgaccactgg	tgctgcagaa	gggcccgtgc	ttacattcca	attaacagac	gcttttccca	780
tctaagtcc	cttgccctct	cctaacacca	cctcgggagt	gtttatgtct	attctaagtg	840
aatttcactg	tgtgaaaaaa	ttcacacctg	ttgtcccagc	gatttgggag	gcccgggcgg	900
gtgtatcatt	tgagcccagg	agtttgaggc	tagcctgggc	aggatgggtga	aaccccgctc	960
ctataaagaa	attttaaaaa	ttagctgggc	atagtggcac	gtgcctgtag	ttccatctac	1020
tggggaggct	ggggtgggag	gatcgcatga	gcccgggagt	ttgaggctgc	agtgagctgt	1080
gatcgacgca	ctgcactcca	gtctgggcaa	cagagcaaga	ccctgtctct	taaaaaaaaa	1140
aaaaaaaaact	cgag					1154

<210> 87
<211> 1197
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (573)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (1177)
<223> n equals a,t,g, or c

<220>
<221> SITE

<222> (1185)

<223> n equals a,t,g, or c

<400> 87

aagacaggaa	aagctccagg	ccgtggttct	caaagtgtgg	tccctggaca	gcagcaacat	60
cacctaggag	cctgttaggg	aaggcacagc	ctcaggccct	gccccagacc	tgcagaatca	120
gaaactctgg	ggtgaggcct	ggttatctgc	tgtaacagac	cttccagtgg	gttctgatgc	180
cctctagagc	aggagaacca	ctagcttaga	ggttgacagta	tgtttggcat	cttgccatct	240
gtgttagttc	agaggaatgg	ctgaccccca	tgtctcattt	ctaagcttca	ggcagctttt	300
ctcctgggca	gctgtcattc	tggtgagggg	aatcctgggg	actgtgggctc	ctcctccctg	360
tccgtgtgtc	cttgatctgg	cagtctaccc	ccttcattctc	cccgtggagg	ctccatgccw	420
agagggtggtc	ttcaaacaga	agaatggcaa	arataattgt	ctcgtgtttt	accctgaccc	480
cattccttta	agagggtcac	ttcttggccc	attcatttaa	aaaccaatgt	catagtctctg	540
tgattccacc	tatcagacag	tgccacgtcc	aangcggggc	tctcacctcc	ctgggaagag	600
agactgttgc	tgtctgtgct	tcctgtgttc	tccagtccca	cgctcccacg	gacccacgcc	660
cttggagact	ccctcagtgt	cccagggtct	ctggtgtgtt	cagagacctc	cacactcaac	720
gaccactggg	gctgcagaag	ggccggtgct	tacattccaa	ttaacagacg	cttttcccat	780
ctaactgcctc	ttgccttctc	ctaaccaccac	ctcgggagtg	tttatgtcta	ttctaagtga	840
atttctactgt	gtgaaaaaat	tcacacctgt	tatcccagca	atttgggagg	ccgaggcggg	900
tgtatcattt	gggcccagga	gtttgagact	agcctgggca	agatggtgaa	accccgtctc	960
tataaagaaa	ttttaaaaaat	tggctgggca	tagtggcgcg	tgccctgtagt	tccatctgct	1020
ggggaggctg	gggtgggagg	atcgcatgag	cccgggagtt	tgaggctgca	gtgagctgtg	1080
atcgcgccac	tgactccag	tctgggcaac	agagcaaaac	cctgtctctt	aaaaaaaaaa	1140
aaaactcgag	ggggggcccg	gtaccaatt	cgccctnats	agtnagtcg	tattaca	1197

<210> 88

<211> 910

<212> DNA

<213> Homo sapiens

<400> 88

ggcagagctg	gccttcgact	cgctatgtcc	actaacaata	tgctggaccc	acggaggccg	60
aacaaagtgc	tgagggtgagg	accccagcgt	cgtagggcacg	ggttcggggt	gtgggtgtgg	120
atcgggggcc	tggaagcgc	ctgtctatcc	cgggggcagg	acctgagcgc	ccctgaccct	180
cgagcctgtc	gcaggtaaca	gccccgcgcg	agcgaatgta	acccggcctt	ggacgacccg	240
acgcccggact	acatgaacct	gctgggcatg	atcttcagca	tgtagcggcct	catgcttaag	300
ctgaagtggg	gtgcttgggt	cgctgtctac	tgctccttca	tcagctttgc	caactctcgg	360
agctcggagg	acacgaagca	aatgatgagt	agcttcatgt	gagacttgcc	ctacagaaca	420
agtgactctt	gagtaagggg	tggggggacc	ccagcctggc	catcctagac	tgacacctct	480
ctcctgtctt	catgctgtcc	atctctgccg	tggtgatgtc	ctatctgcag	aatcctcagc	540
ccatgacgcc	cccatggtga	taccagccta	gaagggtcac	atcttggacc	ctgtctatcc	600
actaggcctg	ggcttgggt	gctaaacctg	ctgccttcag	ctgccatcct	ggacttcctt	660
gaatgaggcc	gtctcgggtc	ccccagctgg	atagaggga	cctggccctt	tcctagggaa	720
caccctaggc	ttacccctcc	tgccctccct	cccctgcctg	ctgctggggg	agatgctgtc	780
catgtttcta	gggtatttca	tttgctttct	cggtgaaacc	tggtgttaat	aaagttttct	840
actctgaaaa	aaaaaaaaaa	aaaaaaaaac	tygrgggggg	gcccggaaac	caattcscgg	900
gatagtgagt						910

<210> 89

<211> 1076

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1029)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1037)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1040)

<223> n equals a,t,g, or c

<400> 89

ggcacgaggg	gaaagccatg	ctcccaggac	tccttccttg	cagccttaa	tcggtctgta	60
cggaataattc	cgcgccttag	aaacccacgc	ttgggtgtaa	cttattattg	ttcttcctga	120
ccfacttct	gtttatcaact	tccgggttca	tcattttggc	atttcggtga	tcgggttgga	180
actattgaag	cccgttttca	ggttcttttc	cccatTTTcc	ctttgaaagg	aagacttctg	240
gcttctccta	aatctccgtt	ctctgggtaa	ggggagtcca	agcctctgtc	atgaggaaacg	300
gaaatgcgag	ggcctcgggt	gttactctaa	aatccgccct	cagcttgcac	gccggaagct	360
gcgattcctg	cagcggaaga	ggcgtgatct	ggccttcgac	tcgctatgtc	actaacaat	420
atgtcggacc	cacggaggcc	gaacaaagtg	ctgaggtaca	agccccgcc	gagcgaatgt	480
aacccggcct	tggacgaccc	gacgccggac	tacatgaacc	tgctgggcat	gatcttcagc	540
atgtgcggcc	tcatgcttaa	gctgaagtgg	tgtgcttggg	tcgctgtcta	ctgctccttc	600
atcagctttg	ccaactctcg	gagctcggag	gacacgaagc	aaatgatgag	tagcttcatg	660
ctgtccatct	ctgccgtggt	gatgtcctat	ctgcagaatc	ctcagcccat	gacgccccca	720
tggtgatacc	agcctagaag	ggtcacattt	tggacctgt	ctatccacta	ggcctgggct	780
ttggctgcta	aacctgctgc	cttcagctgc	catcctggac	ttccctgaat	gaggccgtct	840
cggtgcccc	agctggatag	agggaaacctg	gccctttcct	agggaaacacc	ctaggcttac	900
ccctctgcc	tcccttcccc	tgctgctgc	tgggggagat	gctgtccatg	tttctagggg	960
tattcatttg	ctttctcggt	gaaacctgtt	gttaataaag	tttttcactc	tgaaaaaaaa	1020
aaaaaaaaana	raaaacncgn	ggggggggccc	ggaacccaat	tcscgggata	gtgagt	1076

<210> 90

<211> 1842

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (67)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (98)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (212)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1838)

<223> n equals a,t,g, or c

<400> 90

gcgaccgcgc	ccttcagcta	gctcgctcgc	tcgctctgct	tccttgctgc	cggtgcgca	60
tggtctnngc	gttggcggcg	ctggcggcgc	ctcgagcngc	ctgcgsagcc	ggtaccagca	120
gttgcagaat	gaagaagagt	ctggagaacc	tgaacaggct	gcaggatgat	ctcctccacc	180
ttacagcagc	atttctgcag	agagcgcaca	tnattttgac	tacaaggatg	agtctggggt	240
tccaaagccc	ccatcttaca	atgtagctac	aacactgccc	agttatgatg	aagcggagag	300
gaccaaggct	gaagctacta	tccttttggg	tcctgggaga	gatgaggatt	ttgtgggtcg	360
ggatgatttt	gatgatgctg	accagctgag	gataggaaat	gatgggattt	tcatgttaac	420
ttttttcatg	gcattcctct	ttaactggat	tgggtttttc	ctgtcttttt	gcctgaccac	480
ttcagctgca	ggaaggtatg	gggccatttc	aggatttggg	ctctctctaa	ttaaattggat	540
cctgattgtc	aggttttcca	cctatttccc	tggatatttt	gatggtcagt	actggctctg	600
gtgggtgttc	cttgttttag	gctttctcct	gtttctcaga	ggatttatca	attatgcaaa	660
agttcgggaag	atgccagaaa	ctttctcaaa	tctccccagg	accagagttc	tctttattta	720
ttaaagatgt	tttctggcaa	aggccttctc	gcatttatga	attctctctc	aagaagcaag	780
agaacacctg	caggaagtga	atcaagatgc	agaacacaga	ggaataatca	cctgctttaa	840
aaaaataaag	tactgttgaa	aagatcattt	ctctctattt	gttccctagg	gtaaaaattt	900
aatagttaat	gcagaattct	gtaatcattg	aatcattagt	ggttaatgtt	tgaaaaagct	960
cttgaatca	agtctgtgat	gtattaataa	tgcttatata	attgtttgta	gtcattttta	1020
gtagcatgag	ccatgtccct	gtagtcggta	gggggcagtc	ttgctttatt	catcctccat	1080
ctcaaaaatga	acttgggaatt	aaatattgta	agatatgtat	aatgctggcc	attttaaagg	1140
gggttttctca	aaagttaaac	ttttgttatg	actgtgtttt	tgacataat	ccatatttgc	1200
tgttcaagtt	aatctagaaa	tttattcaat	tctgtatgaa	cacctggaag	caaaatcata	1260
gtgcaaaaat	acatttaagg	tgtggtcaaa	aataagtctt	taattggtaa	ataataagca	1320
ttaatttttt	atagcctgta	ttcacaaatc	tgcggtacct	tattgtacct	aagggattct	1380
aaaggtgttg	tactgtata	aaacagaaag	cactaggata	caaatagaag	ttaattacta	1440
aaatgtaatt	cttgacactc	tttctataat	tagcgttctt	cacccccacc	cccaccccca	1500
cccccttat	tttctttttg	tctcctgggt	attaggccaa	agtctgggag	taaggagagg	1560
attaggtact	taggagcaaa	gaaagaagta	gcttggaact	tttgagatga	tccttaacat	1620
actgtactac	ttgcttttac	aatgtgttag	cagaaaccag	tgggttataa	tgtagaatga	1680
tgtgctttct	gccaagtgg	taattcatct	tggtttgcta	tgttaaaact	gtaaatataa	1740
cagaacatta	ataaatatct	cttgtgtagc	accttttaaa	aaaaaaaaaa	aaaaaaaaaa	1800
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aa		1842

<210> 91

<211> 1963

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (335)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1959)

<223> n equals a,t,g, or c

<400> 91

ggatcctcgc	ggcggcggcg	gtgcttacag	cctgagaaga	gcgtctcgcc	cgggagcggc	60
ggcggccatc	gagacccacc	caaggcgcgt	ccccctcggc	ctccagcgc	tcccaagccg	120
cagcggccgc	gccccttcag	ctagctcgct	cgctcgctct	gcttccctgc	tgccggctgc	180
gcatggcktt	ggcgttggcg	gcgctggcgg	cggtcgagcc	gcctgcgcag	ccggtaccag	240
cagttgcaga	atgaagaaga	gtctggagaa	cctgaacagg	ctgcaggatga	tgctcctcca	300
ccttacagca	gcatttctgc	agagagcgca	gcatnatttt	gactacaagg	atgagtctgg	360
gtttccaaag	cccccatctt	acaatgtagc	tacaacactg	cccagttatg	atgaagcggga	420
gaggaccaag	gctgaagcta	ctatcccttt	ggttctctgg	agagatgagg	attttgtggg	480

57

tcgggatgat	tttcatgatg	ctgaccagct	gaggatagga	aatgatggga	ttttcatggt	540
aacttttttc	atggcattcc	tctttaactg	gattgggttt	ttcctgtctt	tttgcctgac	600
cacttcagct	gcaggaaggt	atggggccat	ttcaggattt	ggctctcttc	taattaaatg	660
gacccctgatt	gtcaggtttt	ccacctat	ccctggatat	tttcatggtc	agtactggct	720
ctgggtgggtg	ttccttgttt	taggttttct	cctgtttctc	agaggattta	tcaattatgc	780
aaaagttcgg	aagatgccag	aaactttctc	aaatctcccc	aggaccagag	ttctctttat	840
ttattaaaga	tgttttctgg	caaaggcctt	cctgcattta	tgaattctct	ctcaagaagc	900
aagagaacac	ctgcaggaag	tgaatcaaga	tcgagaacac	agaggaataa	tcacctgctt	960
taaaaaaata	aagtactgtt	gaaaagatca	tttctctcta	tttgttccta	ggtgtaaaaat	1020
tttaataagt	aatgcagaat	tctgtaatca	ttgaatcatt	agtgggttaat	gtttgaaaaa	1080
gctcttgcaa	tcaagtctgt	gatgtattaa	taatgcctta	tatatgtttt	gtagtcattt	1140
taagtagcat	gagccatgtc	cctgtagtcg	gtagggggca	gtcttgcttt	attcatcttc	1200
catctcaaaa	tgaacttgga	attaaatatt	gtaagatatg	tataatgctg	gccattttta	1260
aggggttttc	tcaaaaagta	aacttttggt	atgactgtgt	ttttgcacat	aatccatatt	1320
tgctgttcaa	gttaatctag	aaatttat	aattctgtat	gaacacctgg	aagcaaaatc	1380
atagtgcata	aatacattta	aggtgtgggtc	aaaaataagt	ctttaattgg	tataataata	1440
gcattaattt	tttatagcct	gtattcacaa	ttctgcggta	ccttattgta	cctaagggat	1500
tctaaagggtg	ttgtcactgt	ataaaacaga	aagcactagg	atacaaatga	agcttaatta	1560
ctaaaatgta	attcttgaca	ctctttctat	aattagcgtt	cttcacccc	acccccaccc	1620
ccacccccct	tattttcctt	ttgtctcctg	gtgattaggc	caaagtcctg	gagtaaggag	1680
aggattaggt	acttaggagc	aaagaaagaa	gtagcttgga	acttttgaga	tgatccctaa	1740
catactgtac	tacttgcttt	tacaatgtgt	tagcagaac	cagtgggtta	taatgtagaa	1800
tgatgtgctt	tctgoccaa	tggttaattca	tcttggtttg	ctatgttaaa	actgtaaata	1860
caacagaaca	ttaataaata	tctcttgtgt	agcaccttta	aaaaaaaaa	aaaaaaaaa	1920
aaaaaaaaa	aaaaaaaaa	aaaaaaaaa	aaaaaaaaa	aaa		1963

<210> 92

<211> 1487

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1470)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1487)

<223> n equals a,t,g, or c

<400> 92

gcgaccgcgc	ccctttcagc	tagctcgctc	gctcgctctg	cttcctctgt	gccggctgcg	60
catggckwtg	gcgttggcgg	cgctggcggc	ggtcgagccg	gcctgcgcag	ccggtaccag	120
cagttgcaga	atgaagaaga	gtctggagaa	cctgaacagg	ctgcagggtga	tgctcctcca	180
ccttacagca	gcatttctgc	agagagcgca	gttttccacc	tatttccctg	gatattttga	240
tggtcagtag	tggtctctgt	gggtgttcct	tgtttttaggc	tttctcctgt	ttctcagagg	300
atttatcaat	tatgcaaaag	ttcggaagat	gccagaaact	ttctcaaatc	tccccaggac	360
cagagttctc	tttatattt	aaagatgttt	tctggcaaa	gccttctctg	atttatgaat	420
tctctctcaa	gaagcaagag	aacacctgca	ggaagtgaat	caagatgcag	aacacagagg	480
aataatcacc	tgcttttaaaa	aaataaaagta	ctgttgaaaa	gatcatttct	ctctatttgt	540
tcttaggtgt	aaaattttta	tagttaatgc	agaattctgt	aatcattgaa	tcattagtgg	600
ttaatgtttg	aaaaagctct	tgcaatcaag	tctgtgatgt	attaataatg	ccttatatat	660
tgttttagt	catttttaagt	agcatgagcc	atgtccctgt	agtcggtagg	gggcagctct	720
gctttattca	tcctccatct	caaaatgaac	ttggaattaa	atattgttaag	atatgtataa	780
tgctggccat	tttaaagggt	ttttctcaaa	agttaaactt	ttgttatgac	tggtgttttg	840
cacataatcc	atatttgctg	ttcaagttaa	tctagaaatt	tattcaattc	tgatgaaca	900

58

cctggaagca	aaatcatagt	gcaaaaatac	atttaagggtg	tgggtcaaaaa	taagtcttta	960
attggtaaat	aataagcatt	aattttttat	agcctgtatt	cacaattctg	cggtacctta	1020
ttgtacctaa	gggattctaa	agggtgtgtc	actgtataaa	acagaaagca	ctaggataca	1080
aatgaagctt	aattactaaa	atgtaattct	tgacactctt	tctataatta	gcgttcttca	1140
ccccaccacc	caccaccacc	ccccttattt	tccttttgtc	tcctgggtgat	taggccaag	1200
tctgggagta	aggagaggat	taggtactta	ggagcaaaga	aagaagtagc	ttggaacttt	1260
tgagatgata	cctaacatac	tgtactactt	gcttttacia	tgtgttagca	gaaaccagtg	1320
gggtataatg	tagaatgatg	tgctttctgc	ccaagtggta	attcatcttg	gtttgctatg	1380
ttaaaactgt	aaatacaaca	gaacattaat	aaatatctct	tgtgtagcac	ctttaaaaaa	1440
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaan	ccccgggggg	ggccccc		1487

<210> 93

<211> 1653

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (67)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (212)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1636)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1653)

<223> n equals a,t,g, or c

<400> 93

gcgaccgcgc	ccttcagcta	gctcgctcgc	tcgctctgct	tcctctgctgc	cggtctgcga	60
tggcttnggc	gttggcgggc	ctggcgggcg	ctcgagccgc	ctgcgsagcc	ggtaccagca	120
gttgacgaat	gaagaagagt	ctggagaacc	tgaacaggct	gcagggtgatg	ctcctccacc	180
ttacagcagc	atttctgcag	agagcgcaca	tnattttgac	tacaaggatg	agtctgggtt	240
tccaaagccc	ccatcttaca	atgtagctac	aacactgccc	agttatgatg	aagcggagag	300
gaccaaggct	gaagctacta	tccctttggt	tcctgggaga	gatgaggatt	ttgtgggtcg	360
ggatgatttt	gatgatgctg	accagctgag	gataggaaat	gatgggattt	tcattgttaac	420
ttttttcatg	gcatttcctct	ttaactggat	tgggtttttc	ctgtcttttt	gcctgaccac	480
ttcagctgca	ggaaggtatg	gggccatttc	aggatttggg	ctctctctaa	ttaaatggat	540
cctgattgtc	aggttttcca	cctatttccc	tgcatattatg	aattctctct	caagaagcaa	600
gagaacacct	gcaggaagtg	aatcaagatg	cagaacacag	aggaataatc	acctgcttta	660
aaaaaataaa	gtactgttga	aaagatcatt	tctctctatt	tgttcctagg	tgtaaaattt	720
taatagttaa	tgcagaattc	tgtaatcatt	gaatcattag	tggttaattg	ttgaaaaagc	780
tcttgcaatc	aagtctgtga	tgtattaata	atgccttata	tattgtttgt	agtcatttta	840
agtagcatga	gccatgtccc	tgtagtcggt	agggggcagt	cttgctttat	tcattcctcca	900
tctcaaaatg	aacttggaat	taaatattgt	aagatatgta	taatgctggc	catttttaag	960
gggttttctc	aaaagttaa	cttttgttat	gactgtgttt	ttgcacataa	tccatatttg	1020
ctgttcaagt	taatctagaa	atttattcaa	ttctgtatga	acacctggaa	gcaaaatcat	1080
agtgcaaaaa	tacatttaag	gtgtgggtcaa	aaataagtct	ttaattggta	aataataagc	1140
attaattttt	tatagcctgt	attcacaatt	ctgcggtacc	ttattgtacc	taagggtatc	1200

59

taaagggtgtt gtcactgtat aaaacagaaa gcactaggat acaaatgaag cttaattact	1260
aaaatgtaat tcttgacact ctttctataa ttagcggttct tcacccccac ccccacccc	1320
acccccctta ttttcctttt gtctcctggt gattaggcca aagtctggga gtaaggagag	1380
gattagggtac ttaggagcaa agaaagaagt agcttggaac ttttgagatg atccctaaca	1440
tactgtacta cttgctttta caatgtgtta gcagaaacca gtgggttata atgtagaatg	1500
atgtgctttc tgcccaagtg gtaattcatc ttggtttgct atgttaaaac tgtaaataca	1560
acagAACatt aataaatatc tcttgtgtag caccttttaw aaaaaaaaaa aaaaaaaaaa	1620
aaaaaaaaaa aaaaancccg ggggggggcc ccn	1653

<210> 94

<211> 1830

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (67)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (97)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (211)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1813)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1830)

<223> n equals a,t,g, or c

<400> 94

gagaccgcgc ccttcagcta gtcgctcgc tcgctctgct tccctgctgc cggctgcgca	60
tggtctnngc gttggcggcg ctggcggcgg tcgagcngcc tgcsagccg gtaccagcag	120
ttgcagaatg aagaagagtc tggagaacct gaacaggctg caggatgatg tcctccacct	180
tacagcagca tttctgcaga gagcgacat natcttgact acaaggatga gtctgggttt	240
ccaaagcccc catcttaca tgtagctaca aactgcccc gttatgatga agcggagagg	300
accaaggctg aagctactat ccctttggtt cctgggagag atgaggattt tgggtgctcg	360
gatgattttg atgatgctga ccagctgagg ataggaaatg atgggatttt catgttaact	420
tttttcatgg cattcctctt taactggatt ggggttttcc tgtctttttg cctgaccact	480
tcagctgcag gaaggatagg ggccatttca ggatttggtc tctctctaata taaatggatc	540
ctgattgtca ggttttccac ctatttccct ggatattttg atggtcagta ctggctctgg	600
tggtgtctcc ttgttttagg ctttctcctg tttctcagag gatttatcaa ttatgcaaaa	660
gttcggaaga tgccagaaac tttctcaaat ctcccagga ccagagttct ctttatttat	720
taaagatgtt ttctggcaaa ggccttctg catttatgaa ttctctctca agaagcaaga	780
gaacacctgc aggaagtga tcaagatgca gaacacagag gaataatcac ctgctttaa	840
aaaataaagt actgttgaaa agatcatttc tctctatttg ttcttaggtg taaaatttta	900
atagttaatg cagaattctg taatcattga atcattagtg gttaatgttt gaaaaagctc	960
ttgcaatcaa gtctgtgatg tattaataat gccttatata ttgtttgtag tcattttaag	1020

60

tagcatgagc	catgtccctg	tagtcggtag	ggggcagctc	tgctttattc	atcctccatc	1080
tcaaaatgaa	cttggaatta	aatattgtaa	gatatgtata	atgctggcca	ttttaaaggg	1140
gttttctcaa	aagttaaact	tttggtatga	ctgtgttttt	gcacataatc	catatttgc	1200
gttcaagtta	atctagaaat	ttattcaatt	ctgtatgaac	acctggaagc	aaaatcatag	1260
tgcaaaaata	catttaaggt	gtggtcaaaa	ataagtcttt	aattggtaaa	taataagcat	1320
taatttttta	tagcctgtat	tcacaattct	gcggtacctt	attgtacctt	agggattcta	1380
aagggtgtgt	cactgtataa	aacagaaagc	actaggatac	aaatgaagct	taattactaa	1440
aatgtaattc	ttgacctctt	ttctataatt	agcgttcttc	acccccaccc	ccacccccac	1500
cccccttatt	ttccttttgt	ctcctggtga	ttaggccaaa	gtctgggagt	aaggagagga	1560
ttaggtactt	aggagcaaag	aaagaagtag	cttggaactt	ttgagatgat	ccctaacata	1620
ctgtactact	tgcttttaca	atgtgttagc	agaaaccagt	gggttataat	gtagaatgat	1680
gtgctttctg	cccaagtggg	aattcatctt	ggtttgctat	gttaaaactg	taaatacaac	1740
agaacattaa	taaataatct	ttgtgtagca	ccttttaaaa	aaaaaaaaaa	aaaaaaaaaa	1800
aaaaaaaaaa	aancccgggg	gggggccccn				1830

<210> 95

<211> 1134

<212> DNA

<213> Homo sapiens

<400> 95

tccatctaca	gtcctcacac	aggtattcag	gaataccagg	atggcgtgcc	caagattcca	60
acagcctgta	ttacggtgga	agatgcagaa	atgatgtcaa	gaatggcttc	tcatgggatc	120
aaaattgtca	ttcagctaaa	gatgggggca	aagacctacc	cagatactga	ttccttcaac	180
actgtagcag	agatcactgg	gagcaaatat	ccagaacagg	ttgtactggt	cagtggacat	240
ctggacagct	gggatgttgg	gcaggggtgcc	atggatgatg	gcggtggagc	ctttatatca	300
tgggaagcac	tctcacttat	taaagatctt	gggctgcgtc	caaagaggac	tctgcggctg	360
gtgctctgga	ctgcagaaga	acaaggtgga	gttgggtgcct	tccagtatta	tcagttacac	420
aagggtaaata	tttccaacta	cagtctggtg	atggagtctg	acgcaggaac	cttcttacct	480
actgggctgc	aattcactgg	cagtgaagg	gccagggcac	catggaggag	gttatgagcc	540
tgctgcagcc	cctcaatatc	actcaggtcc	tgagccatgg	agaagggaca	gacatcaact	600
tttgatcca	agctggagtg	cctggagcca	gtctacttga	tgacttatac	aagtatttct	660
tcttccatca	ctcccacgga	gacaccatga	ctgtcatgga	tccaaagcag	atgaatgttg	720
ctgctgctgt	ttgggctggt	gtttcttatg	ttgttcgaga	catggaagaa	atgctgccta	780
ggcctagaa	acagtaagaa	agaaacgttt	cctgcttctt	ggccaggaat	cctgggtctg	840
caactttgga	aaactcctct	tcacataaca	atttcatacca	attcatcttc	aaagcacaac	900
tctatttcat	gctttctggt	attatctttc	ttgatacttt	ccaaattctc	tgcatcttag	960
aaaaaggaat	cattctcccc	tccctccac	cacatagaat	caacatatgg	tagggattac	1020
agtgggggca	tttctttata	tcacctctta	aaaacattgt	ttccacttta	aaagtaaaca	1080
cttaataaat	ttttggaaga	tctctgaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaa	1134

<210> 96

<211> 1772

<212> DNA

<213> Homo sapiens

<400> 96

tcgaccacg	cgctccgggag	gatccccagc	cgggtcccaa	gcctgtgcct	gagcctgagc	60
ctgagcctga	gccgagccgg	gagccggctg	cgggggctcc	gggctgtggg	accgctgggc	120
ccccagcgat	ggcgaccctg	tggggaggcc	ttcttcggct	tggctccttg	ctcagcctgt	180
cgctcctggc	gctttccgtg	ctgctgctgg	cgcactgtca	gacgccgcca	agaatttcga	240
ggatgtcaga	tgtaaagtga	tctgccctcc	ctataaagaa	aaattctggg	catattttata	300
ataagaacat	atctcagaaa	gattgtgatt	gccttcatgt	tgtggagccc	atgcctgtgc	360
gggggcctga	tgtagaagca	tactgtctac	gctgtgaatg	caaatatgaa	gaaagaagct	420
ctgtcacaat	caaggttacc	attataattt	atctctccat	tttgggcctt	ctacttctgt	480
acatggtata	tcttactctg	gttgagccca	tactgaagag	gcgcctcttt	ggacatgcac	540

61

agttgataca	gagtgatgat	gatattgggg	atcaccagcc	ttttgcaaat	gcacacgatg	600
tgctagcccg	ctccccagtg	cgagccaacg	tgctgaacaa	ggtagaatat	ggcacagcag	660
cgctggaagc	ttcaagtcca	agagcagcga	aaagtctgtc	tttgaccggc	atgttgtcct	720
cagctaattg	gggaattgaa	ttcaagggtga	ctagaaagaa	acaggcagac	aactggaaaag	780
gaactgactg	ggttttgctg	ggtttcattt	taataccttg	ttgatttcac	caactgttgc	840
tggaagattc	aaaactggaa	gkaaaaactt	gcttgatttt	tttttcttgt	taacgtaata	900
atagagacat	ttttaaaagc	acacagctca	aagtcagcca	ataagtcttt	tcctatttgt	960
gacttttact	aataaaaaata	aatctgcctg	taaaataaat	taaaaaatcc	tttacctgga	1020
acaagcactc	tcctttttcac	cacatagttt	taacttgact	ttccaagata	attttcaggg	1080
tttttggtgt	tggtgttttt	tggttggttg	ttttggtggg	agaggggagg	gatgcctggg	1140
aaagtgttaa	caactttttt	caagtcactt	tactaaacaa	acttttgtaa	atagacctta	1200
ccttctattt	tcgagtttca	tttatatttt	gcagtgtagc	cagcctcatc	aaagagctga	1260
cttactcatt	tgacttttgc	actgactgta	ttatctgggt	atctgctgtg	tctgcacttc	1320
atggtaaaacg	ggatctaaaa	tgcttggtgg	cttttcacaa	aaagcagatt	ttcttcatgt	1380
actgtgatgt	ctgatgcaat	gcacccatga	acaaactggc	catttgctag	tttactctaa	1440
agactaaaca	tagtcttggg	gtgtgtgggc	ttactcatct	tctagtacct	ttaaggacaa	1500
atcctaagga	cttggaactt	tgcaataaag	aaattttatt	ttaaacccaa	gcctccctgg	1560
attgataata	tatacacatt	tgtcagcatt	tccggtcgtg	gtgagaggca	gctgtttgag	1620
ctccaatgtg	tgagcttttg	aactagggct	gggtgtgtgg	gtgcctcttc	tgaaagggtc	1680
aaccattatt	ggataactgg	ctttttttct	tcctctttgg	aatgtaacaa	taaaaataat	1740
ttttgaaaca	tcaaaaaaaa	aaaaaaaaaa	aa			1772

<210> 97

<211> 2381

<212> DNA

<213> Homo sapiens

<400> 97

ccacgcgtcc	cgcaaggcca	gttctagtgt	agagagaaaa	aggagccggc	agcggctctt	60
acgcgtcccg	gggctgcgcg	ccactctctc	ggccggtaac	gcggtgcttt	gcggtgtcgc	120
tcaagcgcgg	cgttggggcg	gcgggcgggg	gctgaggggc	tgccatggcg	gcggcggggc	180
ggctcccag	ctcctggggc	ctcttctcgc	cgctccctgc	agggccttga	ctactgggag	240
tcgggcccgg	cccagcgcgg	gcgctgcaca	acgtcacggc	cgagctcttt	ggggccgagg	300
cctggggcac	ccttgccggt	ttcggggacc	tcaactccga	caagcagacg	gatctcttcg	360
tgtctcgggg	aagaaatgac	ttaatcgtct	ttttggcaga	ccagaatgca	ccctatttta	420
aacccaaagt	aaaggatatc	ttcaagaatc	acagtgcatc	gataacaagt	gtagtccctg	480
gggattatga	tgagagattc	caaatggatg	tccttctgac	atatcttccc	aaaaattatg	540
ccaagagtga	attaggagct	gttatcttct	ggggacaaaa	tcaaacatta	gatcctaaca	600
atatgaccat	actcaatagg	acttttcaag	atgagccact	aattatggat	ttcaatgggtg	660
atctaattcc	tgatattttt	ggatccacaa	atgaatccaa	ccagccacag	atactattag	720
gagggaaatt	atcatggcat	ccagcattga	ccactacaag	taaaatgcga	attccacatt	780
ctcatgcatt	tattgatctg	actgaagatt	ttacagcaga	tttattcctg	acgacattga	840
atgccaccac	tagtaccttc	cagtttgaaa	tatgggaaaa	tttgatgga	aacttctctg	900
tcagttactat	attggaaaaa	cctcaaaaata	tgatgggtgg	tgagcagtcg	gcatttgcag	960
actttgatgg	agatggacac	atggatcatt	tactgccagg	ctgtgaagat	aaaaattgcc	1020
aaaagagtac	catctactta	gtgagatctg	ggatgaagca	gtgggttcca	gtcctacaag	1080
atttcagcaa	taagggcaca	ctctggggct	ttgtgccatt	tgtggatgaa	cagcaaccaa	1140
ctgaaatacc	aattccaatt	acccttcata	ttggagacta	caatatggat	ggctatccag	1200
acgctctggt	catactaaag	aacacatctg	gaagcaacca	gcaggccttt	ttactggaga	1260
acgtcccttg	taataatgca	agctgtgaag	aggcgcgtcg	aatgtttaaa	gtctactggg	1320
agctgacaga	cctaaatcaa	attaaggatg	ccatgggtgc	caccttcttt	gacattttacg	1380
aagatggaat	cttggacatt	gtagtgttaa	gtaaaggata	tacaaagaat	gattttgcca	1440
ttcatacact	aaaaaataac	tttgaagcag	atgcttattt	tgttaaagtt	attgttctta	1500
gtggtctgtg	ttctaattgac	tgtcctcgta	gataacaccc	tttgagtgta	atcaacctgg	1560
accttatatc	atgtatacaa	ctgtagatgc	aaatgggtat	ctgaaaaatg	gatcagctgg	1620
ccaactcagc	caatccgcac	atttagctct	ccaactacca	tacaacgtgc	ttggttttagg	1680
tcggagcgca	aattttcttg	accatctcta	cgttggtatt	ccccgtccat	ctggagaaaa	1740

62

atctatacga	aaacaagagt	ggactgcaat	cattccaaat	tcccagctaa	ttgtcattcc	1800
ataccctcac	aatgtccctc	gaagtggag	tgccaaactg	tatcttacac	caagtaatat	1860
tggtctgctt	actgctatag	ctctcatcgg	tgtctgtgtt	ttcatcttgg	caataattgg	1920
cattttacat	tggcaggaaa	agaaagcaga	tgatagagaa	aaacgacaag	aagcccaccg	1980
gttttcatttt	gatgctatgt	gacttgccct	taatatata	taatggaatg	gctgttccct	2040
tgattagtgt	aaacacaaat	tctggcctga	aaaaataggg	gagattaaat	attatttata	2100
aatgatgtat	cccatggtaa	ttattggaaa	gtattcaaat	aaatatgggt	tgaatatgtc	2160
acaaggtctt	ttttttttaa	gcactttgta	tataaaaatt	tgggttctct	attctgtagt	2220
gctgtacatt	tttgttcctt	tgtggaatgt	gttgcatgta	ctccagtgtt	tgtgtattta	2280
taatcttatt	tgcacatga	tgatggaaaa	agttgtgtaa	ataaaaaata	ttaaattgagc	2340
aggaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	a		2381

<210> 98

<211> 1955

<212> DNA

<213> Homo sapiens

<400> 98

ggcacgagt	ccatccctgt	atttgctgcc	atgctcttcc	ttttctccat	ggctacactg	60
ttgaggacca	gcttcagtga	ccctggagtg	attcctcggg	cgctaccaga	tgaagcagct	120
ttcatagaaa	tggagataga	agctaccaat	ggtgcggtgc	cccagggcca	gcgaccaccg	180
cctcgtatca	agaattttca	gataaacaac	cagattgtga	aactgaaata	ctgttacaca	240
tgcaagatct	tccggcctcc	ccgggcctcc	cattgcagca	tctgtgacaa	ctgtgtggag	300
cgcttcgacc	atcactgccc	ctgggtgggg	aattgtgttg	gaaagaggaa	ctaccgctac	360
ttctacctct	tcaccccttc	tctctccctc	ctcacaaatc	atgtcttctc	cttcaacatc	420
gtctatgttg	ccctcaaate	tttgaataat	ggcttcttgg	agacattgaa	aggaaactcc	480
tggaactgtt	ctagaagtcc	tcatttgctt	ctttacactc	tggctccgtc	tgggactgac	540
tggatttcat	actttcctcg	tggctctcaa	ccagacaacc	aatgaaagac	atcaaaggat	600
catggacagg	gaagaatcgc	gtccagaatc	cctacagcca	tggcaatatt	gtgaagaact	660
gctgtgaagt	gctgtgtggc	cccttgcccc	ccagtgtgct	ggatcgaagg	ggatattttgc	720
cactggagga	aagtggaggt	cgacctccca	gtactcaaga	gaccagtagc	agcctcttgc	780
cacagagccc	agccccccaca	gaacacctga	actcaaatga	gatgccggag	gacagcagca	840
ctcccgaaga	gatgccacct	ccagagcccc	cagagccacc	acaggaggca	gctgaagctg	900
agaagtagcc	tatctatgga	agagactttt	gtttgtgttt	aattagggct	atgagagatt	960
tcaggtgaga	agttaaacct	gagacagaga	gcaagtaagc	tgtccctttt	aactgttttt	1020
ctttgtctct	tagtcaccca	gttgacactc	ggcattttct	tgtctgaagc	tttttttaaat	1080
ttctgaactc	aaggcagtg	cagaagatgt	cagtcacctc	tgataactgg	aaaaatgggt	1140
ctcttggggc	ctggcactgg	ttctccatgg	cctcagccac	aggggtcccct	tggaccccct	1200
ctcttccctc	cagatcccag	ccctcctgct	tgggggtcact	ggtctcattc	tgggggctaaa	1260
agtttttcgag	actgggtcaa	atcctcccaa	gctgctgcac	gtgctgagtc	cagaggcagt	1320
cacagagacc	tctggccagg	ggatccctaac	tgggttcttg	gggtcttcag	gactgaagag	1380
gagggagagt	gggtgcagaa	gattctcctg	gccaccaagt	gccagcattg	cccacaaatc	1440
cttttaggaa	tgggacaggt	accttcactc	agttgtattt	attagtgtag	cttctccttt	1500
gtctcccatc	cactctgaca	ccttaagccc	cactcttttc	ccattagata	tatgtaagta	1560
gttgtagtag	agataataat	tgacatttct	cgtagactac	ccagaaactt	ttttaataacc	1620
tgtgccattc	tcaataagaa	tttatgagat	gccagcgcca	tagcccttca	cactctctgt	1680
ctcatctctc	ctcctttctc	attagcccct	tttaatttgt	ttttcctttt	gactcctgct	1740
cccattagga	gcaggaatgg	cagtaataaa	agtctgcact	ttggtcattt	cttttcctca	1800
gaggaagcct	gagtgtcac	ttaaactacta	tcccctcaga	ctccctgtgt	gaggcctgca	1860
gaggccctga	atgcacaaat	gggaaaccaa	ggcacagaga	ggctctcctc	tcctctcctc	1920
tcccccgatg	taccctcaaa	aaaaaaaaaa	aaaaaa			1955

<210> 99

<211> 1958

<212> DNA

<213> Homo sapiens

<400> 99

ccacgcgtcc	ggggcggttc	tggtcgtgag	aggggagccc	caggggagct	ggggcagcat	60
gactgggggtg	ataaatggcc	ggaaatttgg	cgtaggccaca	ctcaacacca	gcgtgatgca	120
ggaggcacac	tccggggtca	gcagcatcca	cagcagcatc	cgccatgtcc	cagcaaacgt	180
ggggcctctg	atgcgggtgc	tcgtggtcac	catcgcccc	atctactggg	ccctggccag	240
agagagtggg	gaagccctga	atggccactc	tctgactggg	ggcaagtcc	ggcagagtca	300
cacgtggagt	ttgctacagg	gagctgctca	cgatgaccca	gtggcccggg	gtctggatcc	360
cgatggcctc	ctgctcctcg	acgtgggtgt	caatggcggt	gtccccggac	gagcctgggt	420
gacgcagatc	ttcaagtgca	ggactttgaa	gaagcactac	gtgcaaaaa	gggcctggcc	480
agctgttcgt	gggctccaca	cagcgcttct	tccaggggcg	cctcccctcg	ttcctacgct	540
gcaaccacac	catccagtac	aacgcggccc	ggggccccc	gccccagctg	gtgcagcacc	600
tgcgggcctc	agctatcagc	tcggcctttg	atccagaggc	cgaggccctg	cgcttccagc	660
tcgctacagc	cctgcaggcg	gaggagaacg	aggtcggctg	ccccgagggc	tttgagctgg	720
actcccaggg	agcgttttgt	gtggatgtgg	acgagtgtgc	gtgggatgct	cacctctgcc	780
gagagggaca	gcgctgtgtg	aaactgtctg	ggtcctaccg	ctgcctcccc	gactgtgggg	840
ctggcttccg	ggtggtctgat	ggggccggct	gtgaaaatgt	ggacgaatgc	ctggaagggg	900
ttggacgact	gtcactacaa	ccagctctgc	gagaacaccc	caggcgggtca	ccgctgcagc	960
tgccccaggg	gttaccggat	gcaggggccc	agcctgccct	gcctagatgt	caatgagtgc	1020
ctgcagctgc	ccaaggcctg	cgctaccag	tgccacaacc	tccagggcag	ctaccgctgc	1080
ctgtgcccc	caggccagac	cctccttcgc	gacggcaagg	cctgcacctc	actggagcgg	1140
aatggacaaa	atgtgaccac	cgtcagccac	cgaggccctc	tattgccctg	gctgcggccc	1200
tgggcctcga	tccccggtac	ctcctaccac	gcctgggtct	ctctccgtcc	gggtcccatg	1260
gccctgagca	gtgtgggccc	ggcctggtgc	cctcctggtt	tcacaggca	gaacggagtc	1320
tgcacagacc	ttgacgagtg	ccgcgtgagg	aacctgtgtc	agcacgcctg	ccgcaacact	1380
gagggcagct	accagtgcct	gtgccccgcc	ggctaccgtc	tgctccccag	cgggaagaac	1440
tgccaggaca	tcaacgagtg	cgaggaggag	agcatcagtg	gtggaccctg	ccagatgtgc	1500
ttcaaacacc	gtggcagcta	ccagtgtgtg	gacacaccct	gtcctgccac	ctaccggcag	1560
ggccccagcc	ctgggacgtg	cttcggcgcc	tgctcgcagg	actgcggcac	gggcggccct	1620
tctacgctgc	agtaccggct	gctgcgcgtg	cccctgggcg	tgcgcgccca	ccacgacgtg	1680
gccccgctca	ccgccttctc	cgaggctggc	gtccccgcca	accgcaccga	gctcagcatg	1740
ctggagcccc	acccccgcag	ccccttcgcg	ctgcgtccgc	tgcgcgcggg	ccttgggcgg	1800
gtctacaccc	gtcgcgcgct	cacccgcgcc	ggcctctacc	ggctcacctg	gcgtgctgcg	1860
gcaccgcgcc	accaaagcgt	cttcgtcttg	ctcatcgccg	tgcccccta	cccctactaa	1920
acgggagagg	gcattggcgg	ccgctctaga	ggatccct			1958

<210> 100

<211> 2444

<212> DNA

<213> Homo sapiens

<400> 100

ttacgccaaag	ctggcacgag	caatgaaaga	gttaatctct	ttggctgggc	ctacagatga	60
catacagagt	acagtcccc	aggttcatgc	tttaaataac	cttagagcat	tggtcagaga	120
tacgcgcctg	ggagaaaata	ttattcctta	tggtgctgat	ggagctaagg	ctgcaattct	180
gggtttttaca	tcaccggtct	gggcagtgcg	aaattcatcc	acacttctct	ttagtgcctt	240
gatcacaaaga	atTTTTggag	ttaaaagggg	aaaggatgaa	cattccaaaa	caaatagaat	300
gacagggaga	gagtttttct	ctcgtttccc	agaactctat	ccttttcttc	tcaaacagtt	360
ggaaactgta	gccaatacag	tagacagtga	tatgggagaa	ccaaatcgte	atccaagcat	420
gtttctctta	cttttgggtg	tggagagact	ctacgcttcc	ccgatggatg	gtacttcttc	480
tgctctcagc	atgggacctt	ttgttccctt	cattatgagg	tggtggtcact	cacctgtcta	540
ccactcccgt	gaaatggcag	ctcgtgcctt	ggtcccatct	gttatgatag	atcacattcc	600
taataccatt	cgaactctgt	tgccacact	ccccagctgc	actgaccagt	gtttccgggc	660
aaaaccacat	tcatggggac	acttctccag	gttttcccat	ttgttgcaag	cctactcaga	720
ctccaaaaca	cggaacgaat	tcagacttcc	agcacgagct	gactgacatc	actgtttgta	780
ccaaagccaa	actctggtcg	gccaagaggc	aaaatccatg	tttggtgacc	agagctgtat	840
atattgatat	tctcttccta	ttgacttgct	gcctcaacag	atctgcaaaag	gacaaccagc	900

cagttctgga	gagtccttggc	ttctgggaag	aaattcaaag	ggaattatct	caggatcaga	960
agctgataac	gggattccct	tgggccttca	aggtgccagg	cctgccccag	tacctccaga	1020
gcctcaccag	actagccatt	gctgcagtgt	gggccgcggc	agccaagagt	ggagagcggg	1080
agacgaatgt	ccccatctct	ttctctcagc	tgtagaatc	tgccctccct	gaagtgcgct	1140
cactaacact	ggaagccctc	ttggaaaagt	tcttagcagc	agactctgga	cttgagagaga	1200
agggcgtgcc	acccttgctg	tgcaacatgg	gagagaagtt	cttattgttg	gccatgaagg	1260
aaaatcacc	agaatgcttc	tgcaagatac	tgaaaattct	acactgcatg	gaccctgggtg	1320
agtggcttcc	ccagacggag	cactgtgtcc	atctgacccc	aaaggagtcc	ttgatctgga	1380
cgatggatat	tgcttccaat	gaaagatctg	aaattcagag	tgtagctctg	agacttgctt	1440
ccaaagtcac	ttcccaccac	atgcagacat	gtgtggagaa	caggggaattg	atagctgctg	1500
agctgaagca	gtgggttcag	ctggtcatct	tgctatgtga	agaccatctt	cctacagagt	1560
caggtctggc	cgctcgttgaa	gtcctcacca	gtactacacc	acttttcctc	accaaccccc	1620
atcctattct	tgagttgcag	gatacacttg	ctctctggaa	gtgtgtcctt	acccttctgc	1680
agagtggaga	gcaagctgtt	agagatgcag	ccacggaaac	cgtagaact	gccatgtcac	1740
aagaaaatac	ctgccagtca	acagagtttg	ccttctgcca	ggtggatgcc	tccatcgctc	1800
tggccctggc	cctggccgtc	ctgtgtgac	tgctccagca	gtgggaccag	ttggcccctg	1860
gactgcccc	cctgctggga	tggctgttgg	gagagagtga	tgacctcgtg	gcctgtgttg	1920
agagcatgca	tcaggtggaa	gaagactacc	tgtttgaaaa	agcagaagtc	aacttttggg	1980
ccgagaccct	gatctttgtg	aaatacctct	gcaagcacct	cttctgtctc	ctctcaaagt	2040
ccggctggcg	tcccccaagc	cctgagatgc	tctgtcacct	tcaaaggatg	gtgtcagagc	2100
agtgccacct	cctgtctcag	ttcttcagag	agcttcacc	agctgctgag	tttgtgaaga	2160
cagtggagtt	cacaagacta	cgcattcaag	aggaaaaggac	tttggcttgc	ttgaggctgc	2220
tggccttttt	ggaaggaaag	gaagggaag	acaccctagt	tctcagtgtt	tgggactcct	2280
atgcagaatc	gaggcagtta	actcttccaa	gaacagaagc	ggcatgttga	agaaaatctg	2340
ggggattggg	atgggggtat	gtgtggattt	ttcctccact	aaatctgcag	gaaacatgtt	2400
gaacataaat	tcaaaaattt	tatcccaaaa	aaaaaaaaaa	aaaa		2444

<210> 101

<211> 2709

<212> DNA

<213> Homo sapiens

<400> 101

ggcacgagat	ttcctacagg	tgaaacgcca	tcattaggat	tcactgtaac	gttagtgcta	60
ttaaactcac	tagcattttt	attaatggcc	gttatctaca	ctaagctata	ctgcaacttg	120
gaaaaagagg	acctctcaga	aaactcaca	tctagcatga	ttaagcatgt	cgcttggtta	180
atcttcacca	attgcattct	tttctgccct	gtggcgtttt	tttcatttgc	accattgatc	240
actgcaatct	ctatcagccc	cgaaataatg	aagtctgtta	ctctgatatt	ttttccatgc	300
ctgcttgcc	gaatccagtc	ctgtatgttt	tcttcaacc	aaagtttaa	gaagactgga	360
agttactgaa	gagcagtggt	accaagaaaa	gtggatcagt	ttcagtttcc	atcagtagcc	420
aagggtggtg	tctggaacag	gatttctact	acgactgtgg	catgtactca	catttgcagg	480
gcaacctgac	tgtttgcgac	tgctgcgaat	cgtttctttt	aacaaagcca	gtatcatgca	540
aacacttgat	aaaatcacac	agctgtcctg	cattggcagt	ggcttcttgc	caaagacctg	600
agggtactag	gtccgactgt	ggcacacatt	cgggccactc	tgattatgca	gatgaagaag	660
attcctttgt	ctcagacagt	tctgaccagg	tgacggcctg	tgagcagacc	tgcttctacc	720
agagtagagg	attccctttg	gtgcgctatg	cttacaatct	accaagagtt	aaagactgaa	780
ctactgtgtg	tgtaaccgtt	tccccgtca	accaaataca	gtgtttatag	agtgaacctt	840
attctcatct	ttcatctggg	aagcacttct	gtaatcactg	cctgggtgtca	cttagaagaa	900
ggagagggtg	cagtttattt	ctcaaaccag	tcattttcaa	agaacagggtg	cctaaattat	960
aaattgggtg	aaaatgcaat	gtccaagcaa	tgtatgatct	gtttgaaaca	aatatatgac	1020
ttgaaaagga	tcttaggtgt	agtagagcaa	tataatgtta	gttttttctg	atccataaga	1080
agcaaattta	tacctatttg	tgtattaagc	acaagataaa	gaacagctgt	taatattttt	1140
taaaaattct	atttttaaaa	tgtgattttc	tataactgaa	gaaaaatatc	ttgctaattt	1200
tacctaatgt	ttcatccttt	aatctcagga	caacttactg	cagggccaaa	aaagggactg	1260
tcccagctag	acctgtgaga	gtatacatag	gcattacttt	attatgtttt	cacttgccat	1320
ccttgacata	agagaactat	aaattttgtt	taagcaattt	ataaatctaa	aacctgaaga	1380
tgttttttaa	acaatatata	cagctgttag	gttaaaaaaa	tagctggaca	tttgttttca	1440

65

gtcattatac	attgcttttg	tccaatcagt	aattttttct	taagtgtttt	gtgattacac	1500
tactagaaaa	aaagtaaaag	gctaattgct	gtgtgggttt	agtcgatttg	gctaaactac	1560
taactaatgt	gggggtttta	tagtatctga	gggatttggt	ggcttcattg	aatgttctca	1620
ttaatgaata	cttctaata	tctgttgctc	tactaatatt	ttccaatttg	ctgggatgtc	1680
acctagcaat	agcttggatt	atatagaaag	taaactgtgg	tcaatacttg	catttaatta	1740
gacgaaacgg	ggagtaatta	tgacacgaag	tacttaatgt	ttatttctta	gtgagctgga	1800
ttatcttgaa	cctgtgctat	taaatggaaa	tttccataca	tcttcccat	actatttttt	1860
ataaaagagc	ctattcaata	gctcagaggt	tgaactctgg	ttaaacaaga	taatattgta	1920
ttaataaaaa	tagaagaaga	aagaataaag	cttagtcctg	tgtcttttaa	aaattaaaaa	1980
ttttacttga	ttccccatct	atgggcttta	gacctattac	tgggtggagt	cttaaagtta	2040
taattgttca	atatgttttt	tgaacagtgt	gctaaatcaa	tagcaaacc	actgccatat	2100
tagttattct	gaatatacta	aaaaaatcca	gctagattgc	agtttaataa	ttaaactgta	2160
catactgtgc	atataatgaa	tttttatctt	atgtaaatta	tttttagaac	acaagtggg	2220
aaatgtggct	tctgttcatt	tctgttaatt	aaagctacct	cctaaactat	agtggctgcc	2280
agtagcagac	tgttaaattg	tgggttatat	actttttgca	ttgtaaatag	tctttgttgt	2340
acattgtcag	tgtataaaaa	acagaatcct	tgtatatcaa	aatcatgtag	ttgtataaaa	2400
atgtgggaag	gatttattta	cagtgtgttg	taattttgta	aggccaacta	tttacaagtt	2460
ttaaaaattg	ctatcatgta	tatttacaca	tctgataaat	attaaatcat	aacttggtta	2520
gaaactccta	attaaaaggt	tttttccaaa	attcagggtta	ttgaaaactt	ttcattttat	2580
tcatttaaaa	actagaataa	cagatatata	aaagtgttaa	tctttgtgct	atatggtagt	2640
aaatacaata	ttgtactcag	tgttttgaat	tattaaagtt	tctagaaagc	aaaaaaaaaa	2700
aaaaaaaaa						2709

<210> 102

<211> 1722

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (401)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (695)

<223> n equals a,t,g, or c

<400> 102

gggaccgcgc	tgtcctgctg	tcaccaagag	ctggagacac	catctccac	cgagagtcac	60
ggccccattg	gcctgcacc	tctcgtcct	cgtcccatc	ctctcagcc	tgggtggctc	120
ccaggactgg	aaggctgaac	gcagccaaga	ccccttcgag	aaatgcatgc	aggatcctga	180
ctatgagcag	ctgctcaagg	tcaccatcct	ggaggcagat	aacaggatcg	ggggccgcat	240
cttcacctac	cgggaccaga	wyacgggctg	gattggggag	ctgggagcca	tgcgcatgcc	300
cagctctcac	aggatcctcc	acaagctctg	ccagggcctg	gggctcaacc	tgaccaagtt	360
caccagctac	gacaagaaca	cgtggacgga	ggtgcacgaa	ntgaagctgc	gcaactatgt	420
ggtggagaag	gtgcccagag	agctgggcta	cgccttgctg	ccccaggaaa	agggccactc	480
gcccgaagac	atctaccaga	tggctctcaa	ccaggccctc	aaagacctca	aggcactggg	540
ctgcagaaaag	gcatgaaga	agtttgaaag	gcacacgctc	ttggaatata	ttctcgggga	600
ggggaacctg	agccggccgg	ccgtgcagct	tctgggagac	gtgatgtccg	aggatggctt	660
cttctatctc	agcttcgccc	aggccctccg	ggccnacagc	tgctcagcg	acagactcca	720
gtacagccgc	atcgtgggtg	gctgggacct	gctgccgcgc	gcgctgctga	gctcgtgtgc	780
cgggcttggt	ctgttgaaac	gcgccgtgg	ggcgatgacc	cagggaccgc	acgatgtgca	840
cgtgcagatc	gagacctctc	ccccggcgcg	gaatctgaag	gtgctgaagg	ccgacgtgg	900
gctgctgacg	gcgagcggac	cggcggtgaa	gcgcatcacc	ttctcgccgc	gctgccccgc	960
cacatgcagg	aggcgctgcg	gaggctgcac	tacgtgccgg	ccaccaaggt	gttcctaagc	1020
ttccgcaggc	ccttctggcg	cgaggagcac	attgaaggcg	gccactcaaa	caccgatcgc	1080

66

```

ccgtcgcgca tgattttcta cccgccgccg cgcgagggcg cgctgctgct ggcctcgtac 1140
acgtgggtcgg acgcggcggc agcgttcgcc ggcttgagcc gggaagaggc gttgcgcttg 1200
gcgctcgacg acgtggcggc attgcacggg cctgtcgtgc gccagctctg ggacggcacc 1260
ggcgtcgtca agcgttgggc ggaggaccag cacagccagg gtggctttgt ggtacagmcg 1320
ccggcgctct ggcaaaccga aaaggatgac tggacgggcc cttatggccg catctacttt 1380
gccggcgagc acaccgccta cccgcacggc tgggtggaga cggcgggtcaa gtcggcgctg 1440
cgcgcgcgcca tcaagatcaa cagccggaag gggcctgcat cggacacggc cagccccgag 1500
gggcacgcat ctgacatgga ggggcagggg catgtgcatg ggggtggccag cagccccctg 1560
catgacctgg caaaggaaga aggcagccac cctccagtcc aaggccagtt atctctccaa 1620
aacacgaccc acacgaggac ctgcgattaa agtattttcg gaaaaaaaaa aaaaaaaaaa 1680
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaagggcgg cc 1722

```

<210> 103

<211> 106

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (14)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (29)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 103

```

Met Gly Ser Leu Ser Gly Cys Ala Leu Pro Phe Cys Leu Xaa Val Phe
  1             5             10             15

```

```

Phe Leu Thr Val Ser Pro Ser Ala Val Gly Leu Leu Xaa Phe Ala Gly
          20             25             30

```

```

Gly Pro Leu Gln Thr Leu Phe Ala Trp Val Ser Pro Val Glu Ala Ala
          35             40             45

```

```

Glu Gln Gln Arg Leu Leu Pro Val Leu Ser Ser Gly Ser Phe Val Ser
          50             55             60

```

```

Glu Gly Thr Cys Gln Met Pro Ala Arg Ala Leu Leu Tyr Glu Val Ser
          65             70             75             80

```

```

Val Gly Pro Tyr Trp Glu Ile Pro Pro Ser Gln Asp Thr Arg Arg Ser
          85             90             95

```

```

Gly Thr Tyr Leu Arg Arg Gln Ser Asp Pro
          100             105

```

<210> 104

<211> 86

<212> PRT

<213> Homo sapiens

<400> 104

```

Met Thr Leu Pro Ser Arg Ala Leu Ala Ser Leu Gly Val Gly Val Trp

```

67

1

5

10

15

Gly Met Leu Arg Leu Asn Gln Val Thr Val Ser Cys Gly Gly Ser Arg
 20 25 30

Trp Ser Ser Arg Val Ala Leu Gly Ala Phe Ser Trp Val Cys Gly Val
 35 40 45

Ala Leu Val Leu Gln Pro Ser Gly Gly Gly Leu Gly Leu Thr Ser Pro
 50 55 60

Ser Glu Gly Cys Trp Glu Gly Glu Leu Ala Leu Ala Val Leu Arg Ala
 65 70 75 80

Pro Gly Gly Ser Pro Ser
 85

<210> 105

<211> 302

<212> PRT

<213> Homo sapiens

<400> 105

Met Ala Arg Ala Arg Gly Ser Pro Cys Pro Pro Leu Pro Pro Gly Arg
 1 5 10 15

Met Ser Trp Pro His Gly Ala Leu Leu Phe Leu Trp Leu Phe Ser Pro
 20 25 30

Pro Leu Gly Ala Gly Gly Gly Gly Val Ala Val Thr Ser Ala Ala Gly
 35 40 45

Gly Gly Ser Pro Pro Ala Thr Ser Cys Pro Val Ala Cys Ser Cys Ser
 50 55 60

Asn Gln Ala Ser Arg Val Ile Cys Thr Arg Arg Asp Leu Ala Glu Val
 65 70 75 80

Pro Ala Ser Ile Pro Val Asn Thr Arg Tyr Leu Asn Leu Gln Glu Asn
 85 90 95

Gly Ile Gln Val Ile Arg Thr Asp Thr Phe Lys His Leu Arg His Leu
 100 105 110

Glu Ile Leu Gln Leu Ser Lys Asn Leu Val Arg Lys Ile Glu Val Gly
 115 120 125

Ala Phe Asn Gly Leu Pro Ser Leu Asn Thr Leu Glu Leu Phe Asp Asn
 130 135 140

Arg Leu Thr Thr Val Pro Thr Gln Ala Phe Glu Tyr Leu Ser Lys Leu
 145 150 155 160

Arg Glu Leu Trp Leu Arg Asn Asn Pro Ile Glu Ser Ile Pro Ser Tyr
 165 170 175

Ala Phe Asn Arg Val Pro Ser Leu Arg Arg Leu Asp Leu Gly Glu Leu

68

180

185

190

Lys Arg Leu Glu Tyr Ile Ser Glu Ala Ala Phe Glu Gly Leu Val Asn
 195 200 205

Leu Arg Tyr Leu Asn Leu Gly Met Cys Asn Leu Lys Asp Ile Pro Asn
 210 215 220

Leu Thr Ala Leu Val Arg Leu Glu Glu Leu Glu Leu Ser Gly Asn Arg
 225 230 235 240

Leu Asp Leu Ile Arg Pro Gly Ser Phe Gln Gly Leu Thr Ser Leu Arg
 245 250 255

Lys Leu Trp Leu Met His Ala Gln Val Ala Thr Ile Glu Arg Asn Ala
 260 265 270

Phe Asp Asp Leu Lys Ser Leu Glu Glu Leu Asn Leu Ser His Asn Asn
 275 280 285

Leu Met Ser Leu Pro His Asp Leu Phe Thr Pro Leu His Arg
 290 295 300

<210> 106

<211> 56

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (56)

<223> Xaa equals stop translation

<400> 106

Met Pro Ser Ser Trp Leu Pro Gly Cys Phe Val Leu Leu Cys Leu Val
 1 5 10 15

Ala Val Gly Cys Gln Leu Arg Glu Trp Gly Val Gly Gly Val Ser Ala
 20 25 30

Val Gly Leu Leu Ala Leu Pro His Leu Gln Val Leu Gly Met Arg Gly
 35 40 45

Arg Gly Leu Ile Ser Gly Gly Xaa
 50 55

<210> 107

<211> 189

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (94)

<223> Xaa equals any of the naturally occurring L-amino acids

69

<400> 107

Met Ala Leu Leu Ser Arg Pro Ala Leu Thr Leu Leu Leu Leu Met
 1 5 10 15

Ala Ala Val Val Arg Cys Gln Glu Gln Ala Gln Thr Thr Asp Trp Arg
 20 25 30

Ala Thr Leu Lys Thr Ile Arg Asn Gly Val His Lys Ile Asp Thr Tyr
 35 40 45

Leu Asn Ala Ala Leu Asp Leu Leu Gly Gly Glu Asp Gly Leu Cys Gln
 50 55 60

Tyr Lys Cys Ser Asp Gly Ser Lys Pro Phe Pro Arg Tyr Gly Tyr Lys
 65 70 75 80

Pro Ser Pro Pro Asn Gly Cys Gly Ser Pro Leu Phe Gly Xaa His Leu
 85 90 95

Asn Ile Gly Ile Pro Ser Leu Thr Lys Cys Cys Asn Gln His Asp Arg
 100 105 110

Cys Tyr Glu Thr Cys Gly Lys Ser Lys Asn Asp Cys Asp Glu Glu Phe
 115 120 125

Gln Tyr Cys Leu Ser Lys Ile Cys Arg Asp Val Gln Lys Thr Leu Gly
 130 135 140

Leu Thr Gln His Val Gln Ala Cys Glu Thr Thr Val Glu Leu Leu Phe
 145 150 155 160

Asp Ser Val Ile His Leu Gly Cys Lys Pro Tyr Leu Asp Ser Gln Arg
 165 170 175

Ala Ala Cys Arg Cys His Tyr Glu Glu Lys Thr Asp Leu
 180 185

<210> 108

<211> 61

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (61)

<223> Xaa equals stop translation

<400> 108

Met Gly Asn Cys Gln Ala Gly His Asn Leu His Leu Cys Leu Ala His
 1 5 10 15

His Pro Pro Leu Val Cys Ala Thr Leu Ile Leu Leu Leu Leu Gly Leu
 20 25 30

Ser Gly Leu Gly Leu Gly Ser Phe Leu Leu Thr His Arg Thr Gly Leu
 35 40 45

70

Arg Thr Leu Thr Ser Pro Arg Thr Gly Ser Leu Phe Xaa
 50 55 60

<210> 109

<211> 128

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (47)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (90)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 109

Met Arg Leu Glu Ser Leu Cys His Leu Cys Leu Ala Cys Leu Phe Phe
 1 5 10 15

Arg Leu Pro Ala Thr Arg Thr Val Tyr Cys Met Asn Glu Ala Glu Ile
 20 25 30

Val Asp Val Ala Leu Gly Ile Leu Ile Glu Ser Arg Lys Gln Xaa Lys
 35 40 45

Ala Cys Glu Gln Pro Ala Leu Ala Gly Ala Asp Asn Pro Glu His Ser
 50 55 60

Pro Pro Cys Ser Val Ser Pro His Thr Ser Ser Gly Ser Ser Ser Glu
 65 70 75 80

Glu Glu Asp Ser Gly Lys Gln Ala Leu Xaa Pro Gly Leu Ser Pro Ser
 85 90 95

Gln Arg Pro Gly Gly Ser Ser Ser Ala Cys Ser Arg Ser Pro Glu Glu
 100 105 110

Glu Glu Glu Glu Asp Val Leu Lys Tyr Val Arg Glu Ile Phe Phe Ser
 115 120 125

<210> 110

<211> 69

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (50)

<223> Xaa equals any of the naturally occurring L-amino acids

71

<220>

<221> SITE

<222> (69)

<223> Xaa>equals=stop=translation

<400> 110

Met Pro His Phe Leu Asp Trp Phe Val Pro Val Tyr Leu Val Ile Ser
 1 5 10 15

Val Leu Ile Leu Val Gly Phe Gly Ala Cys Ile Tyr Tyr Phe Glu Pro
 20 25 30

Gly Leu Gln Glu Ala His Lys Trp Arg Met Gln Arg Pro Leu Val Asp
 35 40 45

Arg Xaa Leu Arg Lys Thr Leu Met Val Arg Asp Asn Leu Ala Phe Gly
 50 55 60

Gly Pro Glu Val Xaa
 65

<210> 111

<211> 123

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (123)

<223> Xaa equals stop translation

<400> 111

Met Ile Gly Gly Ile Thr Cys Ile Leu Ser Leu Ile Cys Ala Leu Ala
 1 5 10 15

Leu Ala Tyr Leu Asp Gln Arg Ala Glu Arg Ile Leu His Lys Glu Gln
 20 25 30

Gly Lys Thr Gly Glu Val Ile Lys Leu Thr Asp Val Lys Asp Phe Ser
 35 40 45

Leu Pro Leu Trp Leu Ile Phe Ile Ile Cys Val Cys Tyr Tyr Val Ala
 50 55 60

Val Phe Pro Phe Ile Gly Leu Gly Lys Val Phe Phe Thr Glu Lys Phe
 65 70 75 80

Gly Phe Ser Ser Gln Ala Ala Ser Ala Ile Asn Ser Val Val Tyr Val
 85 90 95

Ile Ser Ala Pro Met Ser Pro Val Phe Gly Leu Leu Val Asp Lys Thr
 100 105 110

Gly Lys Asn Ile Ile Trp Val Leu Cys Ala Xaa
 115 120

72

<210> 112

<211> 83

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (83)

<223> Xaa equals stop translation

<400> 112

Met Glu Lys Gln Cys Cys Ser His Pro Val Ile Cys Ser Leu Ser Thr
 1 5 10 15

Met Tyr Thr Phe Leu Leu Gly Ala Ile Phe Ile Ala Leu Ser Ser Ser
 20 25 30

Arg Ile Leu Leu Val Lys Tyr Ser Ala Asn Glu Gly Lys Leu Arg Leu
 35 40 45

Gly Ile Cys Met Glu His Phe His Leu Ile Thr His Leu Ser Leu Ala
 50 55 60

Phe Gly Ser Val Ile Tyr Asn Met Glu Ile Ile Met Pro Phe Ala Ser
 65 70 75 80

Cys Glu Xaa

<210> 113

<211> 345

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (53)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (345)

<223> Xaa equals stop translation

<400> 113

Met Asp Phe Leu Val Leu Phe Leu Phe Tyr Leu Ala Ser Val Leu Met
 1 5 10 15

Gly Leu Val Leu Ile Cys Val Cys Ser Lys Thr His Ser Leu Lys Gly
 20 25 30

Leu Ala Arg Gly Gly Ala Gln Ile Phe Ser Cys Ile Ile Pro Glu Cys
 35 40 45

Leu Gln Arg Ala Xaa His Gly Leu Leu His Tyr Leu Phe His Thr Arg
 50 55 60

73

Asn His Thr Phe Ile Val Leu His Leu Val Leu Gln Gly Met Val Tyr
 65 70 75 80

Thr Glu Tyr Thr Trp Glu Val Phe Gly Tyr Cys Gln Glu Leu Glu Leu
 85 90 95

Ser Leu His Tyr Leu Leu Leu Pro Tyr Leu Leu Leu Gly Val Asn Leu
 100 105 110

Phe Phe Phe Thr Leu Thr Cys Gly Thr Asn Pro Gly Ile Ile Thr Lys
 115 120 125

Ala Asn Glu Leu Leu Phe Leu His Val Tyr Glu Phe Asp Glu Val Met
 130 135 140

Phe Pro Lys Asn Val Arg Cys Ser Thr Cys Asp Leu Arg Lys Pro Ala
 145 150 155 160

Arg Ser Lys His Cys Ser Val Cys Asn Trp Cys Val His Arg Phe Asp
 165 170 175

His His Cys Val Trp Val Asn Asn Cys Ile Gly Ala Trp Asn Ile Arg
 180 185 190

Tyr Phe Leu Ile Tyr Val Leu Thr Leu Thr Ala Ser Ala Ala Thr Val
 195 200 205

Ala Ile Val Ser Thr Thr Phe Leu Val His Leu Val Val Met Ser Asp
 210 215 220

Leu Tyr Gln Glu Thr Tyr Ile Asp Asp Leu Gly His Leu His Val Met
 225 230 235 240

Asp Thr Val Phe Leu Ile Gln Tyr Leu Phe Leu Thr Phe Pro Arg Ile
 245 250 255

Val Phe Met Leu Gly Phe Val Val Val Leu Ser Phe Leu Leu Gly Gly
 260 265 270

Tyr Leu Leu Phe Val Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr Asn
 275 280 285

Glu Trp Tyr Arg Gly Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu Val
 290 295 300

Ala Trp Pro Pro Ser Ala Glu Pro Gln Val His Arg Asn Ile His Ser
 305 310 315 320

His Gly Leu Arg Ser Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe Pro
 325 330 335

Cys His Glu Arg Lys Lys Gln Glu Xaa
 340 345

<210> 114

<211> 181

<212> PRT

74

<213> Homo sapiens

<220>

<221> SITE

<222> (110)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 114

Met Ala Asp Pro His Val Ser Phe Leu Ser Phe Arg Gln Leu Phe Ser
 1 5 10 15

Trp Ala Ala Val Ile Leu Leu Arg Gly Ile Leu Gly Thr Val Ala Pro
 20 25 30

Pro Pro Cys Pro Cys Val Leu Asp Leu Ala Val Tyr Pro Leu His Leu
 35 40 45

Pro Val Glu Ala Pro Cys Leu Glu Val Val Phe Lys Gln Lys Asn Gly
 50 55 60

Lys Asp Asn Cys Leu Val Phe Tyr Pro Asp Pro Ile Pro Leu Arg Gly
 65 70 75 80

Ser Leu Leu Gly Pro Phe Ile Lys Asn Gln Cys His Ser Ser Val Ile
 85 90 95

Pro Leu Ser Asp Ser Ala Thr Ser Lys Ala Arg Ala Leu Xaa Leu Pro
 100 105 110

Gly Arg Glu Thr Val Leu Ser Val Leu Pro Val Phe Ser Ser Pro Thr
 115 120 125

Leu Pro Arg Thr His Ala Leu Gly Asp Ser Leu Gly Val Pro Gly Leu
 130 135 140

Leu Val Cys Ser Glu Thr Ser Thr Leu Asn Asp His Trp Cys Cys Arg
 145 150 155 160

Arg Ala Gly Ala Tyr Ile Pro Ile Asn Arg Arg Phe Ser His Leu Met
 165 170 175

Pro Leu Ala Phe Ser
 180

<210> 115

<211> 116

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (116)

<223> Xaa equals stop translation

<400> 115

Met Pro Ser Ser Ser Gly Leu Gly Ser Pro Ser Arg Pro Pro Ser
 1 5 10 15

75

Ser Phe Leu Cys Leu Leu Leu Leu Leu Leu Pro Pro Ala Ala Leu Ala
 20 25 30

Leu Leu Leu Phe Phe Leu Asp Phe Phe Pro Pro Arg Ala Ala Val Ser
 35 40 45

Pro Phe Leu Pro Asp His Cys Ser Ala Arg Gln Pro Arg Val Trp Arg
 50 55 60

Arg Glu Thr Leu Asn Arg Ser Ala Ser Gly Leu Gly Cys Trp Ala Arg
 65 70 75 80

Ser Thr Glu Gln Gly Ala Val Gly Val Ala Thr Gly Thr Val Leu Asp
 85 90 95

Ile Ser Leu Pro Ala Ser Cys Leu Ser Leu Trp Pro Pro Gly Pro Ser
 100 105 110

Gly Gly Ile Xaa
 115

<210> 116

<211> 71

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (71)

<223> Xaa equals stop translation

<400> 116

Met Asn Leu Leu Gly Met Ile Phe Ser Met Cys Gly Leu Met Leu Lys
 1 5 10 15

Leu Lys Trp Cys Ala Trp Val Ala Val Tyr Cys Ser Phe Ile Ser Phe
 20 25 30

Ala Asn Ser Arg Ser Ser Glu Asp Thr Lys Gln Met Met Ser Ser Phe
 35 40 45

Met Leu Ser Ile Ser Ala Val Val Met Ser Tyr Leu Gln Asn Pro Gln
 50 55 60

Pro Met Thr Pro Pro Trp Xaa
 65 70

<210> 117

<211> 64

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (64)

76

<223> Xaa equals stop translation

<400> 117

Met Arg Asp Leu Ser Phe Leu Tyr Thr Leu Leu Trp Leu Pro Glu Ile
 1 5 10 15

Trp Gln Ala Leu Ala Gly Gly Ile Arg Leu Asp Glu Val Glu Leu Leu
 20 25 30

Glu Asn Glu Ala Val Leu Gly Glu Glu Met Arg Leu Tyr Arg Lys Ile
 35 40 45

Asn Glu Val Val Leu Ser Gly Asn Glu Val Val Leu Gly Gly Lys Xaa
 50 55 60

<210> 118

<211> 335

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (335)

<223> Xaa equals stop translation

<400> 118

Met Gly Ile Phe Pro Gly Ile Ile Leu Ile Phe Leu Arg Val Lys Phe
 1 5 10 15

Ala Thr Ala Ala Val Ile Val Ser Gly Val Ser Lys His Leu His Cys
 20 25 30

Ile Ser His Gln Lys Ser Thr Thr Val Ser His Glu Met Ser Gly Leu
 35 40 45

Asn Trp Lys Pro Phe Val Tyr Gly Gly Leu Ala Ser Ile Val Ala Glu
 50 55 60

Phe Gly Thr Phe Pro Val Asp Leu Thr Lys Thr Arg Leu Gln Val Gln
 65 70 75 80

Gly Gln Ser Ile Asp Ala Arg Phe Lys Glu Ile Lys Tyr Arg Gly Met
 85 90 95

Phe His Ala Leu Phe Arg Ile Cys Lys Glu Glu Gly Val Leu Ala Leu
 100 105 110

Tyr Ser Gly Ile Ala Pro Ala Leu Leu Arg Gln Ala Ser Tyr Gly Thr
 115 120 125

Ile Lys Ile Gly Ile Tyr Gln Ser Leu Lys Arg Leu Phe Val Glu Arg
 130 135 140

Leu Glu Asp Glu Thr Leu Leu Ile Asn Met Ile Cys Gly Val Val Ser

77

145 150 155 160
~~Gly Val Ile Ser Ser Thr Ile Ala Asn Pro Thr Asp Val Leu Lys Ile~~
 165 170 175
 Arg Met Gln Ala Gln Gly Ser Leu Phe Gln Gly Ser Met Ile Gly Ser
 180 185 190
 Phe Ile Asp Ile Tyr Gln Gln Glu Gly Thr Arg Gly Leu Trp Arg Gly
 195 200 205
 Val Val Pro Thr Ala Gln Arg Ala Ala Ile Val Val Gly Val Glu Leu
 210 215 220
~~Pro Val Tyr Asp Ile Thr Lys Lys His Leu Ile Leu Ser Gly Met Met~~
~~225 230 235 240~~
 Gly Asp Thr Ile Leu Thr His Phe Val Ser Ser Phe Thr Cys Gly Leu
 245 250 255
 Ala Gly Ala Leu Ala Ser Asn Pro Val Asp Val Val Arg Thr Arg Met
 260 265 270
 Met Asn Gln Arg Ala Ile Val Gly His Val Asp Leu Tyr Lys Gly Thr
 275 280 285
 Val Asp Gly Ile Leu Lys Met Trp Lys His Glu Gly Phe Phe Ala Leu
 290 295 300
 Tyr Lys Gly Phe Trp Pro Asn Trp Leu Arg Leu Gly Pro Trp Asn Ile
 305 310 315 320
 Ile Phe Phe Ile Thr Tyr Glu Gln Leu Lys Arg Leu Gln Ile Xaa
 325 330 335

<210> 119

<211> 221

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (51)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 119

Met Ala Leu Ala Leu Ala Ala Leu Ala Ala Val Glu Pro Ala Cys Gly
 1 5 10 15

Ser Arg Tyr Gln Gln Leu Gln Asn Glu Glu Glu Ser Gly Glu Pro Glu
 20 25 30

Gln Ala Ala Gly Asp Ala Pro Pro Pro Tyr Ser Ser Ile Ser Ala Glu
 35 40 45

Ser Ala Xaa Tyr Phe Asp Tyr Lys Asp Glu Ser Gly Phe Pro Lys Pro
 50 55 60

78

Pro Ser Tyr Asn Val Ala Thr Thr Leu Pro Ser Tyr Asp Glu Ala Glu
65 70 75 80

Arg Thr Lys Ala Glu Ala Thr Ile Pro Leu Val Pro Gly Arg Asp Glu
85 90 95

Asp Phe Val Gly Arg Asp Asp Phe Asp Asp Ala Asp Gln Leu Arg Ile
100 105 110

Gly Asn Asp Gly Ile Phe Met Leu Thr Phe Phe Met Ala Phe Leu Phe
115 120 125

Asn Trp Ile Gly Phe Phe Leu Ser Phe Cys Leu Thr Thr Ser Ala Ala
130 135 140

Gly Arg Tyr Gly Ala Ile Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp
145 150 155 160

Ile Leu Ile Val Arg Phe Ser Thr Tyr Phe Pro Gly Tyr Phe Asp Gly
165 170 175

Gln Tyr Trp Leu Trp Trp Val Phe Leu Val Leu Gly Phe Leu Leu Phe
180 185 190

Leu Arg Gly Phe Ile Asn Tyr Ala Lys Val Arg Lys Met Pro Glu Thr
195 200 205

Phe Ser Asn Leu Pro Arg Thr Arg Val Leu Phe Ile Tyr
210 215 220

<210> 120

<211> 473

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (473)

<223> Xaa equals stop translation

<400> 120

Met Lys Phe Leu Ile Phe Ala Phe Phe Gly Gly Val His Leu Leu Ser
1 5 10 15

Leu Cys Ser Gly Lys Ala Ile Cys Lys Asn Gly Ile Ser Lys Arg Thr
20 25 30

Phe Glu Glu Ile Lys Glu Glu Ile Ala Ser Cys Gly Asp Val Ala Lys
35 40 45

Ala Ile Ile Asn Leu Ala Val Tyr Gly Lys Ala Gln Asn Arg Ser Tyr
50 55 60

Glu Arg Leu Ala Leu Leu Val Asp Thr Val Gly Pro Arg Leu Ser Gly
65 70 75 80

79

Ser Lys Asn Leu Glu Lys Ala Ile Gln Ile Met Tyr Gln Asn Leu Gln
85 90 95

Gln Asp Gly Leu Glu Lys Val His Leu Glu Pro Val Arg Ile Pro His
100 105 110

Trp Glu Arg Gly Glu Glu Ser Ala Val Met Leu Glu Pro Arg Ile His
115 120 125

Lys Ile Ala Ile Leu Gly Leu Gly Ser Ser Ile Gly Thr Pro Pro Glu
130 135 140

Gly Ile Thr Ala Glu Val Leu Val Val Thr Ser Phe Asp Glu Leu Gln
145 150 155 160

Arg Arg Ala Ser Glu Ala Arg Gly Lys Ile Val Val Tyr Asn Gln Pro
165 170 175

Tyr Ile Asn Tyr Ser Arg Thr Val Gln Tyr Arg Thr Gln Gly Ala Val
180 185 190

Glu Ala Ala Lys Val Gly Ala Leu Ala Ser Leu Ile Arg Ser Val Ala
195 200 205

Ser Phe Ser Ile Tyr Ser Pro His Thr Gly Ile Gln Glu Tyr Gln Asp
210 215 220

Gly Val Pro Lys Ile Pro Thr Ala Cys Ile Thr Val Glu Asp Ala Glu
225 230 235 240

Met Met Ser Arg Met Ala Ser His Gly Ile Lys Ile Val Ile Gln Leu
245 250 255

Lys Met Gly Ala Lys Thr Tyr Pro Asp Thr Asp Ser Phe Asn Thr Val
260 265 270

Ala Glu Ile Thr Gly Ser Lys Tyr Pro Glu Gln Val Val Leu Val Ser
275 280 285

Gly His Leu Asp Ser Trp Asp Val Gly Gln Gly Ala Met Asp Asp Gly
290 295 300

Gly Gly Ala Phe Ile Ser Trp Glu Ala Leu Ser Leu Ile Lys Asp Leu
305 310 315 320

Gly Leu Arg Pro Lys Arg Thr Leu Arg Leu Val Leu Trp Thr Ala Glu
325 330 335

Glu Gln Gly Gly Val Gly Ala Phe Gln Tyr Tyr Gln Leu His Lys Val
340 345 350

Asn Ile Ser Asn Tyr Ser Leu Val Met Glu Ser Asp Ala Gly Thr Phe
355 360 365

Leu Pro Thr Gly Leu Gln Phe Thr Gly Ser Glu Lys Ala Arg Ala Ile
370 375 380

Met Glu Glu Val Met Ser Leu Leu Gln Pro Leu Asn Ile Thr Gln Val

80

385

390

395

400

Leu Ser His Gly Glu Gly Thr Asp Ile Asn Phe Trp Ile Gln Ala Gly
 405 410 415

Val Pro Gly Ala Ser Leu Leu Asp Asp Leu Tyr Lys Tyr Phe Phe Phe
 420 425 430

His His Ser His Gly Asp Thr Met Thr Val Met Asp Pro Lys Gln Met
 435 440 445

Asn Val Ala Ala Ala Val Trp Ala Val Val Ser Tyr Val Val Ala Asp
 450 455 460

Met Glu Glu Met Leu Pro Arg Ser Xaa
 465 470

<210> 121

<211> 168

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (168)

<223> Xaa equals stop translation

<400> 121

Met Ala Thr Leu Trp Gly Gly Leu Leu Arg Leu Gly Ser Leu Leu Ser
 1 5 10 15

Leu Ser Cys Leu Ala Leu Ser Val Leu Leu Ala His Cys Gln Thr
 20 25 30

Pro Pro Ser Asp Cys Leu His Val Val Glu Pro Met Pro Val Arg Gly
 35 40 45

Pro Asp Val Glu Ala Tyr Cys Leu Arg Cys Glu Cys Lys Tyr Glu Glu
 50 55 60

Arg Ser Ser Val Thr Ile Lys Val Thr Ile Ile Ile Tyr Leu Ser Ile
 65 70 75 80

Leu Gly Leu Leu Leu Leu Tyr Met Val Tyr Leu Thr Leu Val Glu Pro
 85 90 95

Ile Leu Lys Arg Arg Leu Phe Gly His Ala Gln Leu Ile Gln Ser Asp
 100 105 110

Asp Asp Ile Gly Asp His Gln Pro Phe Ala Asn Ala His Asp Val Leu
 115 120 125

Ala Arg Ser Arg Ser Arg Ala Asn Val Leu Asn Lys Val Glu Tyr Ala
 130 135 140

Gln Gln Arg Trp Lys Leu Gln Val Gln Glu Gln Arg Lys Ser Val Phe
 145 150 155 160

Asp Arg His Val Val Leu Ser Xaa
165

<210> 122
<211> 47
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (47)
<223> Xaa equals stop translation

<400> 122
Met Lys Phe Ile Leu Trp Arg Arg Phe Arg Trp Ala Ile Ile Leu Phe
1 5 10 15

Ile Ile Leu Phe Ile Leu Leu Leu Phe Leu Ala Ile Phe Ile Tyr Ala
20 25 30

Phe Pro Asn Tyr Ala Ala Met Lys Leu Val Lys Pro Phe Ser Xaa
35 40 45

<210> 123
<211> 108
<212> PRT
<213> Homo sapiens

<400> 123
Met His Gln Asp Trp Leu Cys Asn Leu Gly Trp Pro Leu Leu Ser Leu
1 5 10 15

Trp Ala Ala Glu Ser Ala Pro His Val Ala Met Ala Ser Ala Thr Ala
20 25 30

Gln Leu Trp Ser Arg Pro Cys Gly Arg Thr His Met Val Ser Leu Ala
35 40 45

Leu Gly His Gln Glu Thr Gly Leu Trp Leu Cys Ser Ala Phe Gly Cys
50 55 60

Val Val Asp Ser Pro Trp Ala Ser Val Cys Pro Ser Val Lys Gly Gln
65 70 75 80

Leu Thr Val Cys Gly Ile Leu Pro Arg Val Pro Val Cys Val Tyr Val
85 90 95

Cys Ala Cys Val Arg Val Ser Met Cys Val His Ile
100 105

<210> 124
<211> 60
<212> PRT
<213> Homo sapiens

82

<400> 124

Met Arg Gly Cys Val Pro Ala Phe Leu Leu His Val Leu Ser Leu Arg
 1 5 10 15

Arg Ala Cys Cys Thr Gln Ala Ala Gln Val Phe Thr Ala Gln Leu Pro
 20 25 30

Gly Arg Gln Val Ala Arg Arg Arg Gly Gly Trp His Glu Gln Gln Gly
 35 40 45

Gly Pro Met Leu Cys Ser Ser His His Ser Arg Thr
 50 55 60

<210> 125

<211> 248

<212> PRT

<213> Homo sapiens

<400> 125

Met Ala Met Leu Pro Leu Val Leu His Trp Phe Phe Ile Glu Trp Tyr
 1 5 10 15

Ser Gly Lys Lys Ser Ser Ser Ala Leu Phe Gln His Ile Thr Ala Leu
 20 25 30

Phe Glu Cys Ser Met Ala Ala Ile Ile Thr Leu Leu Val Ser Asp Pro
 35 40 45

Val Gly Val Leu Tyr Ile Arg Ser Cys Arg Val Leu Met Leu Ser Asp
 50 55 60

Trp Tyr Thr Met Leu Tyr Asn Pro Ser Pro Asp Tyr Val Thr Thr Val
 65 70 75 80

His Cys Thr His Glu Ala Val Tyr Pro Leu Tyr Thr Ile Val Phe Ile
 85 90 95

Tyr Tyr Ala Phe Cys Leu Val Leu Met Met Leu Leu Arg Pro Leu Leu
 100 105 110

Val Lys Lys Ile Ala Cys Gly Leu Gly Lys Ser Asp Arg Phe Lys Ser
 115 120 125

Ile Tyr Ala Ala Leu Tyr Phe Phe Pro Ile Leu Thr Val Leu Gln Ala
 130 135 140

Val Gly Gly Gly Leu Leu Tyr Tyr Ala Phe Pro Tyr Ile Ile Leu Val
 145 150 155 160

Leu Ser Leu Val Thr Leu Ala Val Tyr Met Ser Ala Ser Glu Ile Glu
 165 170 175

Asn Cys Tyr Asp Leu Leu Val Arg Lys Lys Arg Leu Ile Val Leu Phe
 180 185 190

Ser His Trp Leu Leu His Ala Tyr Gly Ile Ile Ser Ile Ser Arg Val

83

195

200

205

Asp Lys Leu Glu Gln Asp Leu Pro Pro Leu Ala Leu Val Pro Thr Pro
 210 215 220

Ala Leu Phe Tyr Leu Phe Thr Ala Lys Phe Thr Glu Pro Ser Arg Ile
 225 230 235 240

Leu Ser Glu Gly Ala Asn Gly His
 245

<210> 126

<211> 248

<212> PRT

<213> Homo sapiens

<400> 126

Met Glu Lys Ile Pro Glu Ile Gly Lys Phe Gly Glu Lys Ala Pro Pro
 1 5 10 15

Ala Pro Ser His Val Trp Arg Pro Ala Ala Leu Phe Leu Thr Leu Leu
 20 25 30

Cys Leu Leu Leu Leu Ile Gly Leu Gly Val Leu Ala Ser Met Phe His
 35 40 45

Val Thr Leu Lys Ile Glu Met Lys Lys Met Asn Lys Leu Gln Asn Ile
 50 55 60

Ser Glu Glu Leu Gln Arg Asn Ile Ser Leu Gln Leu Met Ser Asn Met
 65 70 75 80

Asn Ile Ser Asn Lys Ile Arg Asn Leu Ser Thr Thr Leu Gln Thr Ile
 85 90 95

Ala Thr Lys Leu Cys Arg Glu Leu Tyr Ser Lys Glu Gln Glu His Lys
 100 105 110

Cys Lys Pro Cys Pro Arg Arg Trp Ile Trp His Lys Asp Ser Cys Tyr
 115 120 125

Phe Leu Ser Asp Asp Val Gln Thr Trp Gln Glu Ser Lys Met Ala Cys
 130 135 140

Ala Ala Gln Asn Ala Ser Leu Leu Lys Ile Asn Asn Lys Asn Ala Leu
 145 150 155 160

Glu Phe Ile Lys Ser Gln Ser Arg Ser Tyr Asp Tyr Trp Leu Gly Leu
 165 170 175

Ser Pro Glu Glu Asp Ser Thr Arg Gly Met Arg Val Asp Asn Ile Ile
 180 185 190

Asn Ser Ser Ala Trp Val Ile Arg Asn Ala Pro Asp Leu Asn Asn Met
 195 200 205

Tyr Cys Gly Tyr Ile Asn Arg Leu Tyr Val Gln Tyr Tyr His Cys Thr

84

210	215	220
Tyr Lys Gln Arg Met Ile Cys Glu Lys Met Ala Asn Pro Val Gln Leu		
225	230	235 240

Gly Ser Thr Tyr Phe Arg Glu Ala
245

<210> 127
<211> 612
<212> PRT
<213> Homo sapiens

<220>
<221> SITE-
<222> (245)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (246)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (249)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 127
Met Ala Ala Ala Gly Arg Leu Pro Ser Ser Trp Ala Leu Phe Ser Pro
1 5 10 15

Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
20 25 30

Ala Leu His Asn Val Thr Ala Glu Leu Phe Gly Ala Glu Ala Trp Gly
35 40 45

Thr Leu Ala Ala Phe Gly Asp Leu Asn Ser Asp Lys Gln Thr Asp Leu
50 55 60

Phe Val Leu Arg Glu Arg Asn Asp Leu Ile Val Phe Leu Ala Asp Gln
65 70 75 80

Asn Ala Pro Tyr Phe Lys Pro Lys Val Lys Val Ser Phe Lys Asn His
85 90 95

Ser Ala Leu Ile Thr Ser Val Val Pro Gly Asp Tyr Asp Gly Asp Ser
100 105 110

Gln Met Asp Val Leu Leu Thr Tyr Leu Pro Lys Asn Tyr Ala Lys Ser
115 120 125

Glu Leu Gly Ala Val Ile Phe Trp Gly Gln Asn Gln Thr Leu Asp Pro
130 135 140

Asn Asn Met Thr Ile Leu Asn Arg Thr Phe Gln Asp Glu Pro Leu Ile

85

145		150		155		160
Met Asp Phe Asn Gly Asp Leu Ile Pro Asp Ile Phe Gly Ile Thr Asn						
	165		170		175	
<hr/>						
Glu Ser Asn Gln Pro Gln Ile Leu Leu Gly Gly Asn Leu Ser Trp His						
	180		185		190	
Pro Ala Leu Thr Thr Thr Ser Lys Met Arg Ile Pro His Ser His Ala						
	195		200		205	
Phe Ile Asp Leu Thr Glu Asp Phe Thr Ala Asp Leu Phe Leu Thr Thr						
	210		215		220	
Leu Asn Ala Thr Thr Ser Thr Phe Gln Phe Glu Ile Trp Glu Asn Leu						
225		230		235		240
<hr/>						
Asp Gly Asn Phe Xaa Xaa Ser Thr Xaa Leu Glu Lys Pro Gln Asn Met						
	245		250		255	
Met Val Val Gly Gln Ser Ala Phe Ala Asp Phe Asp Gly Asp Gly His						
	260		265		270	
Met Asp His Leu Leu Pro Gly Cys Glu Asp Lys Asn Cys Gln Lys Ser						
	275		280		285	
Thr Ile Tyr Leu Val Arg Ser Gly Met Lys Gln Trp Val Pro Val Leu						
	290		295		300	
Gln Asp Phe Ser Asn Lys Gly Thr Leu Trp Gly Phe Val Pro Phe Val						
305		310		315		320
Asp Glu Gln Gln Pro Thr Glu Ile Pro Ile Pro Ile Thr Leu His Ile						
	325		330		335	
Gly Asp Tyr Asn Met Asp Gly Tyr Pro Asp Ala Leu Val Ile Leu Lys						
	340		345		350	
Asn Thr Ser Gly Ser Asn Gln Gln Ala Phe Leu Leu Glu Asn Val Pro						
	355		360		365	
Cys Asn Asn Ala Ser Cys Glu Glu Ala Arg Arg Met Phe Lys Val Tyr						
	370		375		380	
Trp Glu Leu Thr Asp Leu Asn Gln Ile Lys Asp Ala Met Val Ala Thr						
385		390		395		400
Phe Phe Asp Ile Tyr Glu Asp Gly Ile Leu Asp Ile Val Val Leu Ser						
	405		410		415	
Lys Gly Tyr Thr Lys Asn Asp Phe Ala Ile His Thr Leu Lys Asn Asn						
	420		425		430	
Phe Glu Ala Asp Ala Tyr Phe Val Lys Val Ile Val Leu Ser Gly Leu						
	435		440		445	
Cys Ser Asn Asp Cys Pro Arg Lys Ile Thr Pro Phe Gly Val Asn Gln						
	450		455		460	

86

Pro Gly Pro Tyr Ile Met Tyr Thr Thr Val Asp Ala Asn Gly Tyr Leu
 465 470 475 480

Lys Asn Gly Ser Ala Gly Gln Leu Ser Gln Ser Ala His Leu Ala Leu
 485 490 495

Gln Leu Pro Tyr Asn Val Leu Gly Leu Gly Arg Ser Ala Asn Phe Leu
 500 505 510

Asp His Leu Tyr Val Gly Ile Pro Arg Pro Ser Gly Glu Lys Ser Ile
 515 520 525

Arg Lys Gln Glu Trp Thr Ala Ile Ile Pro Asn Ser Gln Leu Ile Val
 530 535 540

Ile Pro Tyr Pro His Asn Val Pro Arg Ser Trp Ser Ala Lys Leu Tyr
 545 550 555 560

Leu Thr Pro Ser Asn Ile Val Leu Leu Thr Ala Ile Ala Leu Ile Gly
 565 570 575

Val Cys Val Phe Ile Leu Ala Ile Ile Gly Ile Leu His Trp Gln Glu
 580 585 590

Lys Lys Ala Asp Asp Arg Glu Lys Arg Gln Glu Ala His Arg Phe His
 595 600 605

Phe Asp Ala Met
 610

<210> 128
 <211> 447
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (8)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (28)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (309)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (333)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 128

87

Met Glu Leu Ser Gln Met Ser Xaa Leu Met Gly Leu Ser Val Leu Leu
 1 5 10 15

Gly Leu Leu Ala Leu Met Ala Thr Ala Val Xaa Arg Gly Trp Leu
 20 25 30

Arg Ala Gly Glu Glu Arg Ser Gly Arg Pro Ala Cys Gln Lys Ala Asn
 35 40 45

Gly Phe Pro Pro Asp Lys Ser Ser Gly Ser Lys Lys Gln Lys Gln Tyr
 50 55 60

Gln Arg Ile Arg Lys Glu Lys Pro Gln Gln His Asn Phe Thr His Arg
 65 70 75 80

Leu Leu Ala Ala Ala Leu Lys Ser His Ser Gly Asn Ile Ser Cys Met
 85 90 95

Asp Phe Ser Ser Asn Gly Lys Tyr Leu Ala Thr Cys Ala Asp Asp Arg
 100 105 110

Thr Ile Arg Ile Trp Ser Thr Lys Asp Phe Leu Gln Arg Glu His Arg
 115 120 125

Ser Met Arg Ala Asn Val Glu Leu Asp His Ala Thr Leu Val Arg Phe
 130 135 140

Ser Pro Asp Cys Arg Ala Phe Ile Val Trp Leu Ala Asn Gly Asp Thr
 145 150 155 160

Leu Arg Val Phe Lys Met Thr Lys Arg Glu Asp Gly Gly Tyr Thr Phe
 165 170 175

Thr Ala Thr Pro Glu Asp Phe Pro Lys Lys His Lys Ala Pro Val Ile
 180 185 190

Asp Ile Gly Ile Ala Asn Thr Gly Lys Phe Ile Met Thr Ala Ser Ser
 195 200 205

Asp Thr Thr Val Leu Ile Trp Ser Leu Lys Gly Gln Val Leu Ser Thr
 210 215 220

Ile Asn Thr Asn Gln Met Asn Asn Thr His Ala Ala Val Ser Pro Cys
 225 230 235 240

Gly Arg Phe Val Ala Ser Cys Gly Phe Thr Pro Asp Val Lys Val Trp
 245 250 255

Glu Val Cys Phe Gly Lys Lys Gly Glu Phe Gln Glu Val Val Arg Ala
 260 265 270

Phe Glu Leu Lys Gly His Ser Ala Ala Val His Ser Phe Ala Phe Ser
 275 280 285

Asn Asp Ser Arg Arg Met Ala Ser Val Ser Lys Asp Gly Thr Trp Lys
 290 295 300

Leu Trp Asp Thr Xaa Val Glu Tyr Lys Lys Lys Gln Asp Pro Tyr Leu

Leu Lys Thr Gly Arg Phe Glu Glu Ala Ala Gly Ala Xaa Pro Cys Arg

305 310 315 320

_____ 325 _____ 330 _____ 335

Ser Ile His Leu Tyr Asn Thr Arg Arg Gly Glu Lys Glu Glu Cys Phe
355 360 365

Gly Arg Phe Leu Ala Ser Cys Gly Asp Arg Ala Val Arg Leu Phe His
385 390 395 400

Lys Arg Ala Ser Asn Glu Ser Thr Arg Gln Arg Leu Gln Gln Gln Leu
420 425 430

```
<210> 129
<211> 291
<212> PRT
<213> Homo sapiens
```

<400> 129
Met Leu Phe Leu Phe Ser Met Ala Thr Leu Leu Arg Thr Ser Phe Ser
1 5 10 15

Asp Pro Gly Val Ile Pro Arg Ala Leu Pro Asp Glu Ala Ala Phe Ile
20 25 30

Glu Met Glu Ile Glu Ala Thr Asn Gly Ala Val Pro Gln Gly Gln Arg
35 40 45

Pro Pro Pro Arg Ile Lys Asn Phe Gln Ile Asn Asn Gln Ile Val Lys
50 55 60

Leu Lys Tyr Cys Tyr Thr Cys Lys Ile Phe Arg Pro Pro Arg Ala Ser
65 70 75 80

His Cys Ser Ile Cys Asp Asn Cys Val Glu Arg Phe Asp His His Cys
85 90 95

Pro Trp Val Gly Asn Cys Val Gly Lys Arg Asn Tyr Arg Tyr Phe Tyr
100 105 110

Leu Phe Ile Leu Ser Leu Ser Leu Leu Thr Ile Tyr Val Phe Ala Phe
115 120 125

Asn Ile Val Tyr Val Ala Leu Lys Ser Leu Lys Ile Gly Phe Leu Glu

89

130

135

140

Thr Leu Lys Glu Thr Pro Gly Thr Val Leu Glu Val Leu Ile Cys Phe
 145 150 155 160

Phe Thr Leu Trp Ser Val Val Gly Leu Thr Gly Phe His Thr Phe Leu
 165 170 175

Val Ala Leu Asn Gln Thr Thr Asn Glu Asp Ile Lys Gly Ser Trp Thr
 180 185 190

Gly Lys Asn Arg Val Gln Asn Pro Tyr Ser His Gly Asn Ile Val Lys
 195 200 205

Asn Cys Cys Glu Val Leu Cys Gly Pro Leu Pro Pro Ser Val Leu Asp
 210 215 220

Arg Arg Gly Ile Leu Pro Leu Glu Glu Ser Gly Ser Arg Pro Pro Ser
 225 230 235 240

Thr Gln Glu Thr Ser Ser Ser Leu Leu Pro Gln Ser Pro Ala Pro Thr
 245 250 255

Glu His Leu Asn Ser Asn Glu Met Pro Glu Asp Ser Ser Thr Pro Glu
 260 265 270

Glu Met Pro Pro Pro Glu Pro Pro Glu Pro Pro Gln Glu Ala Ala Glu
 275 280 285

Ala Glu Lys
 290

<210> 130

<211> 78

<212> PRT

<213> Homo sapiens

<400> 130

Met Val Arg Lys Trp Leu Thr Phe Val Glu His Leu Leu Cys Ala Trp
 1 5 10 15

Pro Arg Leu Gly Ala Phe Val Pro Arg Val Thr Pro Ser Glu Cys Ser
 20 25 30

Ser Leu Pro His Ser Asn Trp Gly Val Gly Gly Arg Ala Ala Gln Leu
 35 40 45

Thr Gly Ala Glu Leu Lys Thr His Ser Trp Val Cys Leu Gly Trp Ala
 50 55 60

Val Leu Val Ala Pro Val Ala Asn Thr Arg Ala Pro Phe Thr
 65 70 75

<210> 131

<211> 333

<212> PRT

90

<213> Homo sapiens

<220>

<221> SITE

<222> (97)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 131

Met Leu Met Phe Ala Val Ile Val Ala Ser Ser Gly Leu Leu Leu Met
 1 5 10 15

Ile Glu Arg Gly Ile Leu Ala Glu Met Lys Pro Leu Pro Leu His Pro
 20 25 30

Pro Gly Arg Glu Gly Thr Ala Trp Arg Gly Lys Ala Pro Lys Pro Gly
 35 40 45

Gly Leu Ser Leu Arg Ala Gly Asp Ala Asp Leu Gln Val Arg Gln Asp
 50 55 60

Val Arg Asn Arg Thr Leu Arg Ala Val Cys Gly Gln Pro Gly Met Pro
 65 70 75 80

Arg Asp Pro Trp Asp Leu Pro Val Gly Gln Arg Arg Thr Leu Leu Arg
 85 90 95

Xaa Ile Leu Val Ser Asp Arg Tyr Arg Phe Leu Tyr Cys Tyr Val Pro
 100 105 110

Lys Val Ala Cys Ser Asn Trp Lys Arg Val Met Lys Val Leu Ala Gly
 115 120 125

Val Leu Asp Ser Val Asp Val Arg Leu Lys Met Asp His Arg Ser Asp
 130 135 140

Leu Val Phe Leu Ala Asp Leu Arg Pro Glu Glu Ile Arg Tyr Arg Leu
 145 150 155 160

Gln His Tyr Phe Lys Phe Leu Phe Val Arg Glu Pro Leu Glu Arg Leu
 165 170 175

Leu Ser Ala Tyr Arg Asn Lys Phe Gly Glu Ile Arg Glu Tyr Gln Gln
 180 185 190

Arg Tyr Gly Ala Glu Ile Val Arg Arg Tyr Arg Ala Gly Ala Gly Pro
 195 200 205

Ser Pro Ala Gly Asp Asp Val Thr Phe Pro Glu Phe Leu Arg Tyr Leu
 210 215 220

Val Asp Glu Asp Pro Glu Arg Met Asn Glu His Trp Met Pro Val Tyr
 225 230 235 240

His Leu Cys Gln Pro Cys Ala Val His Tyr Asp Phe Val Gly Ser Tyr
 245 250 255

Glu Arg Leu Glu Ala Asp Ala Asn Gln Val Leu Glu Trp Val Arg Ala
 260 265 270

Pro Pro His Val Arg Phe Pro Ala Arg Gln Ala Trp Tyr Arg Pro Ala
 275 280 285

Ser Pro Glu Ser Leu His Tyr His Leu Cys Ser Ala Pro Arg Ala Leu
 290 295 300

Leu Gln Asp Val Leu Pro Lys Tyr Ile Leu Asp Phe Ser Leu Phe Ala
 305 310 315 320

Tyr Pro Leu Pro Asn Val Thr Lys Glu Ala Cys Gln Gln
 325 330

<210> 132

<211> 164

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (126)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 132

Met Leu Pro Leu Leu Ile Ile Cys Leu Leu Pro Ala Ile Glu Gly Lys
 1 5 10 15

Asn Cys Leu Arg Cys Trp Pro Glu Leu Ser Ala Leu Ile Asp Tyr Asp
 20 25 30

Leu Gln Ile Leu Trp Val Thr Pro Gly Pro Pro Thr Glu Leu Ser Gln
 35 40 45

Ser Ile His Ser Leu Phe Leu Glu Asp Asn Asn Phe Leu Lys Pro Trp
 50 55 60

Tyr Leu Asp Arg Asp His Leu Glu Glu Glu Thr Ala Lys Phe Phe Thr
 65 70 75 80

Gln Val His Gln Ala Ile Lys Thr Leu Arg Asp Asp Lys Thr Val Leu
 85 90 95

Leu Glu Glu Ile Tyr Thr His Lys Asn Leu Phe Thr Glu Arg Leu Asn
 100 105 110

Lys Ile Ser Asp Gly Leu Lys Glu Lys Gly Ala Pro Pro Xaa Ser Met
 115 120 125

Asn Ala Phe Pro Ala Pro Ser Pro Thr Cys Thr Pro Glu Pro Leu Gly
 130 135 140

Ser Val Cys Leu Pro Ser Thr Ser Val Ser Leu Pro Ser His Leu Pro
 145 150 155 160

Gly Ser Leu Gln

<210> 133

<211> 245

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (245)

<223> Xaa equals stop translation

<400> 133

Met Val Ala Val Gly Val Tyr Ala Arg Leu Met Lys His Ala Glu Ala
 1 5 10 15

Ala Leu Ala Cys Leu Ala Val Asp Pro Ala-Ile Leu Leu Ile Val Val
 20 25 30

Gly Val Leu Met Phe Leu Leu Thr Phe Cys Gly Cys Ile Gly Ser Leu
 35 40 45

Arg Glu Asn Ile Cys Leu Leu Gln Thr Phe Ser Leu Cys Leu Thr Ala
 50 55 60

Val Phe Leu Leu Gln Leu Ala Ala Gly Ile Leu Gly Phe Val Phe Ser
 65 70 75 80

Asp Lys Ala Arg Gly Lys Val Ser Glu Ile Ile Asn Asn Ala Ile Val
 85 90 95

His Tyr Arg Asp Asp Leu Asp Leu Gln Asn Leu Ile Asp Phe Gly Gln
 100 105 110

Lys Lys Phe Ser Cys Cys Gly Gly Ile Ser Tyr Lys Asp Trp Ser Gln
 115 120 125

Asn Met Tyr Phe Asn Cys Ser Glu Asp Asn Pro Ser Arg Glu Arg Cys
 130 135 140

Ser Val Pro Tyr Ser Cys Cys Leu Pro Thr Pro Asp Gln Ala Val Ile
 145 150 155 160

Asn Thr Met Cys Gly Gln Gly Met Gln Ala Phe Asp Tyr Leu Glu Ala
 165 170 175

Ser Lys Val Ile Tyr Thr Asn Gly Cys Ile Asp Lys Leu Val Asn Trp
 180 185 190

Ile His Ser Asn Leu Phe Leu Leu Gly Gly Val Ala Leu Gly Leu Ala
 195 200 205

Ile Pro Gln Leu Val Gly Ile Leu Leu Ser Gln Ile Leu Val Asn Gln
 210 215 220

Ile Lys Asp Gln Ile Lys Leu Gln Leu Tyr Asn Gln Gln His Arg Ala
 225 230 235 240

Asp Pro Trp Tyr Xaa

93

245

<210> 134
 <211> 56
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (56)
 <223> Xaa equals stop translation

<400> 134
 Met Gly Thr Val Gly Leu Trp Pro Ser Trp Leu Trp Leu Pro Ala Ser
 1 5 10 15
 Trp Pro Leu Thr Ser Cys Gly Val Thr Arg Arg Arg Leu Arg Gly Pro
 20 25 30
 Gly Leu Arg Arg Thr Ser Gln Thr Gly Arg His Thr Ser Pro Cys Pro
 35 40 45
 Thr Ala Thr Trp Ala Glu Ser Xaa
 50 55

<210> 135
 <211> 55
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (47)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (51)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (55)
 <223> Xaa equals stop translation

<400> 135
 Met Ser Ile Val Met Ser Pro Leu Leu Leu Pro Ile Cys Tyr Leu Asn
 1 5 10 15
 Leu Leu Leu Phe Phe Val Asn Leu Ala Lys Asn Leu Ser Ile Leu Phe
 20 25 30
 Val Ser Ser Lys Lys Tyr Thr Phe Val Phe Met Ile Ser Leu Xaa Phe
 35 40 45
 Phe His Xaa Tyr Phe Ile Xaa

94

50

55

<210> 136

<211> 89

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (89)

<223> Xaa equals stop translation

<400> 136

Met Ala Ile Ile Ser Phe Glu Leu Leu Phe Leu Met Asn Leu Pro Thr
 1 5 10 15

Val Asn Ser Ser Asn Phe Lys Leu Ile Ile Pro Glu Asp Val Thr Leu
 20 25 30

Ser Phe Val Ser His Leu Asp Ile Thr Val Asn His Phe Val Phe Leu
 35 40 45

Ser Thr Phe Glu Leu Ala Gly Val Ile Glu Gly Lys Pro Leu Pro Asp
 50 55 60

Ser Lys Ser Asp Leu Cys Pro Ile Leu Gly Gln Leu Trp Phe His Ile
 65 70 75 80

Leu Leu Phe Phe Ile Phe Trp Val Xaa
 85

<210> 137

<211> 62

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (62)

<223> Xaa equals stop translation

<400> 137

Met Arg Leu Pro Ile Ala Pro His Leu Gln Tyr Phe Met Trp Ser Val
 1 5 10 15

Leu Leu Phe Leu Val Ile Leu Val Asp Met Lys Trp His Leu Ser Val
 20 25 30

Ala Phe His Tyr Ile Ser Leu Met Thr Asn Gly Ile Leu Ser Pro Phe
 35 40 45

Gln Cys Leu Leu Ala Ile His Val Ser Leu Phe Phe Val Xaa
 50 55 60

<210> 138

95

<211> 106

<212> PRT

<213> ~~Homo sapiens~~

<220>

<221> SITE

<222> (106)

<223> Xaa equals stop translation

<400> 138

Met Cys Leu Leu Pro Gly Gly Val Leu Leu Ile Trp Ser Cys Ala Ser
 1 5 10 15

Gly Thr Pro Ala Ser His Thr Lys Asp Trp Gly Arg Cys Lys Phe Ser
 20 25 30

Ala Ala Thr Lys Arg Thr Ala Glu Ser Asn Leu Glu Ser Thr Gln Leu
 35 40 45

Met Leu Ala Ser Gln Ile Asp Pro Leu Leu Ala Glu Cys Trp His Leu
 50 55 60

Cys Ala Ser Val Ser Ser Ser Val Asn Gly Gly Asp Lys Lys Cys Val
 65 70 75 80

His Thr Ser Arg Ala Val Gly Arg Ile Lys Leu Cys Ser Asp Thr Ile
 85 90 95

Arg Ala Cys Ser Gly Trp Tyr Leu Gln Xaa
 100 105

<210> 139

<211> 52

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (52)

<223> Xaa equals stop translation

<400> 139

Met Ser His Ser Val Phe Ala His Tyr Ile Phe Asn Ile Leu Leu Leu
 1 5 10 15

Leu Leu Leu Leu Leu Ile Gly Phe Leu Tyr Ser Met Pro Phe Ile
 20 25 30

Tyr Lys Asp Thr Lys Lys Thr His Val Cys Asn Phe Asn Asn Ile Phe
 35 40 45

Pro Ile Leu Xaa
 50

<210> 140

<211> 119

96

<212> PRT
 <213> Homo sapiens

<400> 140

Met Lys Trp Arg Arg Lys Ser Ala Tyr Trp Lys Ala Leu Lys Val Phe
 1 5 10 15
 Lys Leu Pro Val Glu Phe Leu Leu Leu Leu Thr Val Pro Val Val Asp
 20 25 30
 Pro Asp Lys Asp Asp Gln Asn Trp Lys Arg Pro Leu Asn Cys Leu His
 35 40 45
 Leu Val Ile Ser Pro Leu Val Val Val Leu Thr Leu Gln Ser Gly Thr
 50 55 60
 Tyr Gly Val Tyr Glu Ile Gly Gly Leu Val Pro Val Trp Val Val Val
 65 70 75 80
 Val Ile Ala Gly Thr Ala Leu Ala Ser Val Thr Phe Phe Ala Thr Ser
 85 90 95
 Asp Ser Gln Pro Pro Arg Leu His Trp Leu Phe Ala Phe Leu Gly Phe
 100 105 110
 Leu Thr Ser Ala Leu Trp Ile
 115

<210> 141

<211> 59

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (59)

<223> Xaa equals stop translation

<400> 141

Met Cys Ser Gly Ser Phe Lys Glu Leu Tyr Leu Val Pro Ile Ser Leu
 1 5 10 15
 Phe Ser Thr Cys Val Leu Gly Phe Tyr Phe His Asn Phe Leu Leu Leu
 20 25 30
 Ile Ile Leu Phe Ser Ile Leu Leu Arg Lys Ile Thr Gly Lys Leu Phe
 35 40 45
 Phe Thr Tyr Tyr His Phe Ser Cys Gly Val Xaa
 50 55

<210> 142

<211> 100

<212> PRT

<213> Homo sapiens

97

<220>

<221> SITE

<222> (100)

<223> Xaa equals stop translation

<400> 142

Met Leu Phe Phe Leu Ser Leu Phe Leu Ser Leu Leu Leu Thr Leu Ser
 1 5 10 15

Leu Pro Ser Phe Leu Pro Phe Ser Phe Phe Phe Ser Leu Phe Pro
 20 25 30

His Leu Ser Ala Cys Leu Leu Pro Ser Leu Pro Ser Pro Pro Phe Pro
 35 40 45

Leu Pro Pro Ser Leu Pro Ser Phe Leu Pro Ser Phe Leu Pro Ser Phe
 50 55 60

Leu Pro Ser Leu Leu Ser Pro Ser Phe Pro Ala Phe Phe Pro Ser Phe
 65 70 75 80

Cys Gln Leu Ala Arg Arg Ser Pro Arg Lys Ser Thr Gln Met Leu Gln
 85 90 95

Ser Thr Ser Xaa
 100

<210> 143

<211> 65

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (61)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (65)

<223> Xaa equals stop translation

<400> 143

Met Ala Val Leu Leu Ile Thr Ile Leu Leu Phe Leu Cys Leu Gly Tyr
 1 5 10 15

Tyr Arg Val Ile Thr Glu Ile Ser Arg Lys Thr Pro Ala Cys Arg Met
 20 25 30

Phe Thr Ser Ser Leu Ser Ser Trp Tyr Ile Met Arg Lys Leu Tyr Asp
 35 40 45

Thr Pro Gly Glu Val Phe Leu Ser His Ala Ile Val Xaa Phe Leu Lys
 50 55 60

Xaa
 65

<210> 144

<211> 67

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (67)

<223> Xaa equals stop translation

<400> 144

Met Leu Asn Gln Pro Cys Ile Leu Gly Met Lys Pro Thr Trp Leu Trp

1 5 10 15

Trp Ile Ser Phe Leu Met Cys Cys Trp Val Trp Leu Ala Ser Val Leu

20 25 30

Leu Gly Ile Phe Ala Ser Ile Phe Ile Arg Asp Ile Gly Leu Glu Phe

35 40 45

Ser Phe Phe Val Met Cys Leu Pro Gly Phe Gly Ile Arg Val Met Leu

50 55 60

Ala Ser Xaa

65

<210> 145

<211> 59

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (59)

<223> Xaa equals stop translation

<400> 145

Met Thr Ala Met Ser Ile His Leu Phe Cys Thr Ala Leu Ser Cys Gly

1 5 10 15

Ser Ser Gly Gln Cys Asn Lys Ala Ile Lys Arg Asn Lys Ile Ser Asn

20 25 30

Asp Trp Lys Asp Val Asn Val Ser Ser Phe Ile Glu Asn Met Ile His

35 40 45

Arg Tyr Thr Tyr Thr Asn Ala Leu Asn Ser Xaa

50 55

<210> 146

<211> 56

<212> PRT

<213> Homo sapiens

99

<220>

<221> SITE

<222> (56)

<223> Xaa equals stop translation

<400> 146

Met Ser His Cys Thr Trp Pro Val Cys Leu Phe Cys Leu Val Pro Pro
 1 5 10 15

Pro Met Gly Asp Leu Lys Glu Val Cys Leu Pro His Arg Cys Pro Gly
 20 25 30

Arg Thr Ala Cys Cys Ser Tyr Ser Glu Pro His Leu Gln Thr Glu Glu
 35 40 45

Asp Arg Arg Thr Leu Ile Cys Xaa
 50 55

<210> 147

<211> 66

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (66)

<223> Xaa equals stop translation

<400> 147

Met Thr Asn Gly His Gln Val Leu Leu Leu Leu Leu Thr Ser Ala
 1 5 10 15

Val Ala Ala Gly Pro Trp Pro Gln Val His Ala Gly Gln Trp Gly Trp
 20 25 30

Met Cys Leu Pro Pro Gly Leu Pro Ser Val Gln Ala Arg Ser Gly Leu
 35 40 45

Gly Gly Leu Pro Gly Gly Pro Gln Trp Val Pro Gly Gly Ala Arg Gly
 50 55 60

Tyr Xaa
 65

<210> 148

<211> 328

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (328)

<223> Xaa equals stop translation

<400> 148

Met Ala Cys Arg Lys Leu Ala Val Ala His Pro Leu Leu Leu Arg

1	5	10	15
His Leu Pro Met Ile Ala Ala Leu Leu	His Gly Arg Thr His Leu Asn	100	
20	25	30	
Phe Gln Glu Phe Arg Gln Gln Asn His Leu Ser Cys Phe Leu His Val			
35	40	45	
Leu Gly Leu Leu Glu Leu Leu Gln Pro His Val Phe Arg Ser Glu His			
50	55	60	
Gln Gly Ala Leu Trp Asp Cys Leu Leu Ser Phe Ile Arg Leu Leu Leu			
65	70	75	80
Asn Tyr Arg Lys Ser Ser Arg His Leu Ala Ala Phe Ile Asn Lys Phe			
85	90	95	
Val Gln Phe Ile His Lys Tyr Ile Thr Tyr Asn Ala Pro Ala Ala Ile			
100	105	110	
Ser Phe Leu Gln Lys His Ala Asp Pro Leu His Asp Leu Ser Phe Asp			
115	120	125	
Asn Ser Asp Leu Val Met Leu Lys Ser Leu Leu Ala Gly Leu Ser Leu			
130	135	140	
Pro Ser Arg Asp Asp Arg Thr Asp Arg Gly Leu Asp Glu Glu Gly Glu			
145	150	155	160
Glu Glu Ser Ser Ala Gly Ser Leu Pro Leu Val Ser Val Ser Leu Phe			
165	170	175	
Thr Pro Leu Thr Ala Ala Glu Met Ala Pro Tyr Met Lys Arg Leu Ser			
180	185	190	
Arg Gly Gln Thr Val Glu Asp Leu Leu Glu Val Leu Ser Asp Ile Asp			
195	200	205	
Glu Met Ser Arg Arg Arg Pro Glu Ile Leu Ser Phe Phe Ser Thr Asn			
210	215	220	
Leu Gln Arg Leu Met Ser Ser Ala Glu Glu Cys Cys Arg Asn Leu Ala			
225	230	235	240
Phe Ser Leu Ala Leu Arg Ser Met Gln Asn Ser Pro Ser Ile Ala Ala			
245	250	255	
Ala Phe Leu Pro Thr Phe Met Tyr Cys Leu Gly Ser Gln Asp Phe Glu			
260	265	270	
Val Val Gln Thr Ala Leu Arg Asn Leu Pro Glu Tyr Ala Leu Leu Cys			
275	280	285	
Gln Glu His Ala Ala Val Leu Leu His Arg Ala Phe Leu Val Gly Met			
290	295	300	
Tyr Gly Gln Met Asp Pro Ser Ala Gln Ile Ser Glu Ala Leu Arg Ile			
305	310	315	320

Leu His Met Glu Ala Val Met Xaa
325

<210> 149
<211> 90
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (10)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (13)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (90)
<223> Xaa equals stop translation

<400> 149
Met Gly Phe Leu Gln Leu Leu Val Val Xaa Val Leu Xaa Ser Glu His
1 5 10 15
Arg Val Ala Gly Ala Ala Glu Val Phe Gly Asn Ser Ser Glu Gly Leu
20 25 30
Ile Glu Phe Ser Val Gly Lys Phe Arg Tyr Phe Glu Leu Asn Arg Pro
35 40 45
Phe Pro Glu Glu Ala Ile Leu His Asp Ile Ser Ser Asn Val Thr Phe
50 55 60
Leu Ile Phe Gln Ile His Ser Gln Tyr Gln Asn Thr Thr Val Ser Phe
65 70 75 80
Ser Pro Arg Arg Arg Ser Pro Thr Met Xaa
85 90

<210> 150
<211> 149
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (149)
<223> Xaa equals stop translation

<400> 150
Met Ala Gly Ser Pro Leu Leu Trp Gly Pro Arg Ala Gly Gly Val Gly
1 5 10 15

102

Leu Leu Val Leu Leu Leu Gly Leu Phe Arg Pro Pro Pro Ala Leu
 20 25 30

Cys Ala Arg Pro Val Lys Glu Pro Arg Gly Leu Ser Ala Ala Ser Pro
 35 40 45

Pro Leu Ala Arg Leu Ala Leu Leu Ala Ala Ser Gly Gly Gln Cys Pro
 50 55 60

Glu Val Arg Arg Arg Gly Arg Cys Arg Pro Gly Ala Gly Ala Gly Ala
 65 70 75 80

Ser Ala Gly Ala Glu Arg Gln Glu Arg Ala Arg Ala Glu Ala Gln Arg
 85 90 95

Leu Arg Ile Ser Arg Arg Ala Ser Trp Arg Ser Cys Cys Ala Ser Gly
 100 105 110

Ala Pro Pro Ala Thr Leu Ile Arg Leu Trp Ala Trp Thr Thr Thr Pro
 115 120 125

Thr Arg Leu Gln Arg Ser Ser Leu Ala Leu Cys Ser Ala Pro Ala Leu
 130 135 140

Thr Leu Pro Pro Xaa
 145

<210> 151

<211> 391

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (391)

<223> Xaa equals stop translation

<400> 151

Met Leu Pro Thr Trp Trp Ile Val Ser Ser Trp Leu Val Trp Gly Val
 1 5 10 15

Ile Leu Phe Val Tyr Leu Val Ile Arg Ala Leu Arg Leu Trp Arg Thr
 20 25 30

Ala Lys Leu Gln Val Thr Leu Lys Lys Tyr Ser Val His Leu Glu Asp
 35 40 45

Met Ala Thr Asn Ser Arg Ala Phe Thr Asn Leu Val Arg Lys Ala Leu
 50 55 60

Arg Leu Ile Gln Glu Thr Glu Val Ile Ser Arg Gly Phe Thr Leu Val
 65 70 75 80

Ser Ala Ala Cys Pro Phe Asn Lys Ala Gly Gln His Pro Ser Gln His
 85 90 95

103

Leu Ile Gly Leu Arg Lys Ala Val Tyr Arg Thr Leu Arg Ala Asn Phe
 100 105 110

Gln Ala Ala Arg Leu Ala Thr Leu Tyr Met Leu Lys Asn Tyr Pro Leu
 115 120 125

Asn Ser Glu Ser Asp Asn Val Thr Asn Tyr Ile Cys Val Val Pro Phe
 130 135 140

Lys Glu Leu Gly Leu Gly Leu Ser Glu Glu Gln Ile Ser Glu Glu Glu
 145 150 155 160

Ala His Asn Phe Thr Asp Gly Phe Ser Leu Pro Ala Leu Lys Val Leu
 165 170 175

Phe Gln Leu Trp Val Ala Gln Ser Ser Glu Phe Phe Arg Arg Leu Ala
 180 185 190

Leu Leu Leu Ser Thr Ala Asn Ser Pro Pro Gly Pro Leu Leu Thr Pro
 195 200 205

Ala Leu Leu Pro His Arg Ile Leu Ser Asp Val Thr Gln Gly Leu Pro
 210 215 220

His Ala His Ser Ala Cys Leu Glu Glu Leu Lys Arg Ser Tyr Glu Phe
 225 230 235 240

Tyr Arg Tyr Phe Glu Thr Gln His Gln Ser Val Pro Gln Cys Leu Ser
 245 250 255

Lys Thr Gln Gln Lys Ser Arg Glu Leu Asn Asn Val His Thr Ala Val
 260 265 270

Arg Ser Leu Gln Leu His Leu Lys Ala Leu Leu Asn Glu Val Ile Ile
 275 280 285

Leu Glu Asp Glu Leu Glu Lys Leu Val Cys Thr Lys Glu Thr Gln Glu
 290 295 300

Leu Val Ser Glu Ala Tyr Pro Ile Leu Glu Gln Lys Leu Lys Leu Ile
 305 310 315 320

Gln Pro His Val Gln Ala Ser Asn Asn Cys Trp Glu Glu Ala Ile Ser
 325 330 335

Gln Val Asp Lys Leu Leu Arg Arg Asn Thr Asp Lys Lys Gly Lys Pro
 340 345 350

Glu Ile Ala Cys Glu Asn Pro His Cys Thr Val Ser Thr Phe Glu Ala
 355 360 365

Ala Tyr Ser Thr His Cys Arg Gln Arg Ser Asn Pro Arg Gly Ala Gly
 370 375 380

Ile Arg Ser Leu Cys Arg Xaa
 385 390

104

<210> 152

<211> 99

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (99)

<223> Xaa equals stop translation

<400> 152

Met Thr Thr Arg Gln Pro Thr Ala Val Ser Trp Pro Cys Trp Leu Met
 1 5 10 15

Ser Ser Ser Leu Ser Thr Ala Cys Leu Ala Trp Thr Leu Thr Gly Ser
 20 25 30

Leu Ala Arg Glu Ala Thr Arg Arg Ala Arg Ser Leu Ser Pro Thr Trp
 35 40 45

Asn Cys Ser Ala Arg Gln Val Pro Pro Ser Pro Pro His Ser Gly Leu
 50 55 60

Gly Arg Arg Gly Trp Ala His Cys His Leu Thr Cys Leu Leu Val Thr
 65 70 75 80

Gln Leu Phe Arg Val Gly Arg Ile His Pro Ile Leu Ser Leu Pro Leu
 85 90 95

Val Thr Xaa

<210> 153

<211> 61

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (61)

<223> Xaa equals stop translation

<400> 153

Met Ser His Cys Ala Arg Pro Thr Phe Leu Thr Leu Leu Leu Ala Ser
 1 5 10 15

Cys Phe Trp Ala Ala Ala Ile Pro Asn Arg Asn Val Ile Leu Ser Val
 20 25 30

Ser Phe Arg Pro Leu His Met Gln Phe Thr Leu Ser Ile Leu Val Phe
 35 40 45

Ile Leu Arg Ile Leu Ile Leu Leu Arg Ser Phe Leu Xaa
 50 55 60

<210> 154

105

<211> 393
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (393)
 <223> Xaa equals stop translation

<400> 154

Met Glu Trp Trp Ala Ser Ser Pro Leu Arg Leu Trp Leu Leu Leu Phe
 1 5 10 15

Leu Leu Pro Ser Ala Gln Gly Arg Gln Lys Glu Ser Gly Ser Lys Trp
 20 25 30

Lys Val Phe Ile Asp Gln Ile Asn Arg Ser Leu Glu Asn Tyr Glu Pro
 35 40 45

Cys Ser Ser Gln Asn Cys Ser Cys Tyr His Gly Val Ile Glu Glu Asp
 50 55 60

Leu Thr Pro Phe Arg Gly Gly Ile Ser Arg Lys Met Met Ala Glu Val
 65 70 75 80

Val Arg Arg Lys Leu Gly Thr His Tyr Gln Ile Thr Lys Asn Arg Leu
 85 90 95

Tyr Arg Glu Asn Asp Cys Met Phe Pro Ser Arg Cys Ser Gly Val Glu
 100 105 110

His Phe Ile Leu Glu Val Ile Gly Arg Leu Pro Asp Met Glu Met Val
 115 120 125

Ile Asn Val Arg Asp Tyr Pro Gln Val Pro Lys Trp Met Glu Pro Ala
 130 135 140

Ile Pro Val Phe Ser Phe Ser Lys Thr Ser Glu Tyr His Asp Ile Met
 145 150 155 160

Tyr Pro Ala Trp Thr Phe Trp Glu Gly Gly Pro Ala Val Trp Pro Ile
 165 170 175

Tyr Pro Thr Gly Leu Gly Arg Trp Asp Leu Phe Arg Glu Asp Leu Val
 180 185 190

Arg Ser Ala Ala Gln Trp Pro Trp Lys Lys Lys Asn Ser Thr Ala Tyr
 195 200 205

Phe Arg Gly Ser Arg Thr Ser Pro Glu Arg Asp Pro Leu Ile Leu Leu
 210 215 220

Ser Arg Lys Asn Pro Lys Leu Val Asp Ala Glu Tyr Thr Lys Asn Gln
 225 230 235 240

Ala Trp Lys Ser Met Lys Asp Thr Leu Gly Lys Pro Ala Ala Lys Asp
 245 250 255

106

Val His Leu Val Asp His Cys Lys Tyr Lys Tyr Leu Phe Asn Phe Arg
 260 265 270

~~Gly Val Ala Ala Ser Phe Arg Phe Lys His Leu Phe Leu Cys Gly Ser~~
 275 280 285

Leu Val Phe His Val Gly Asp Glu Trp Leu Glu Phe Phe Tyr Pro Gln
 290 295 300

Leu Lys Pro Trp Val His Tyr Ile Pro Val Lys Thr Asp Leu Ser Asn
 305 310 315 320

Val Gln Glu Leu Leu Gln Phe Val Lys Ala Asn Asp Asp Val Ala Gln
 325 330 335

Glu Ile Ala Glu Arg Gly Ser Gln Phe Ile Arg Asn His Leu Gln Met
 340 345 350

Asp Asp Ile Thr Cys Tyr Trp Glu Asn Leu Leu Ser Glu Tyr Ser Lys
 355 360 365

Phe Leu Ser Tyr Asn Val Thr Arg Arg Lys Gly Tyr Asp Gln Ile Ile
 370 375 380

Pro Lys Met Leu Lys Thr Glu Leu Xaa
 385 390

<210> 155

<211> 75

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (75)

<223> Xaa equals stop translation

<400> 155

Met Leu Ile Leu Phe Leu Ser Val Cys Leu Phe Val Phe Leu Leu Thr
 1 5 10 15

Val Arg Ala Leu Cys Cys Arg Ser Ala Gly Val Trp Leu Arg Ser Thr
 20 25 30

Pro Asp Pro Val Cys Leu Gly Phe Ala Arg Gly Gly Cys Arg Ile Ala
 35 40 45

Met Ile Ala Ala Cys Phe Ser Ser Gly Ser Phe Val Pro Glu Gly His
 50 55 60

Pro Pro Asp Ala Ser Gln Ser Ser Pro Val Xaa
 65 70 75

<210> 156

<211> 82

<212> PRT

107

<213> Homo sapiens

<220>

<221> SITE

<222> (82)

<223> Xaa equals stop translation

<400> 156

Met Trp Pro Leu Leu Ala Val Ser Pro Phe Gly Leu Val Trp Ala Ser
 1 5 10 15

Ser Gln Ser Gly Ser Leu Leu Leu Arg Ala Ser Ile Pro Arg Gln His
 20 25 30

Ser Arg Arg Ala Trp His Phe Tyr Ser Glu Val Trp Gln Ser His Ser
 35 40 45

Val Ala Ser Val Leu Leu Tyr Leu Leu Val Arg Ala Ile Thr Lys Met
 50 55 60

Cys Ile Gly Ser Lys Lys Arg Asp Ile Thr Pro Thr Thr Arg Trp Lys
 65 70 75 80

Lys Xaa

<210> 157

<211> 54

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (49)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (54)

<223> Xaa equals stop translation

<400> 157

Met Ser His His Ala Gly Leu Gly Gly Gly Ile Leu Phe Ser Leu Lys
 1 5 10 15

Ile Ser Phe Phe Ile Ala Leu Ala Val Val Gly Gly Ser Arg Gly Val
 20 25 30

Asn Asp Cys Gln Leu Gly Gly Cys Arg Val Gly Ser Cys Pro Arg Val
 35 40 45

Xaa Val Arg Val Ala Xaa
 50

<210> 158

<211> 103

108

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (103)

<223> Xaa equals stop translation

<400> 158

Met Thr Val Arg Arg Leu Ser Leu Leu Cys Arg Asp Leu Trp Ala Leu
 1 5 10 15

Trp Leu Leu Leu Lys Ala Gly Ala Val Arg Gly Ala Arg Ala Gly Pro
 20 25 30

Arg Leu Pro Gly Arg Cys Cys Gly Ala Thr Cys Gly Asp Ala Gly Arg
 35 40 45

Gly Trp Thr Phe Trp Ala Gln Pro Cys Pro Gln Lys Leu Leu Gly Gln
 50 55 60

Lys Pro Gly Ala Gly Gly Cys Arg Gly Trp Val Leu Gly Trp Val Pro
 65 70 75 80

Pro Arg Pro Glu Glu Pro Cys Ser Leu Ala Gly Lys Val Cys Thr Gly
 85 90 95

Leu Ala Arg Trp Met Val Xaa
 100

<210> 159

<211> 575

<212> PRT

<213> Homo sapiens

<400> 159

Met Arg Val Leu Val Val Thr Ile Ala Pro Ile Tyr Trp Ala Leu Ala
 1 5 10 15

Arg Glu Ser Gly Glu Ala Leu Asn Gly His Ser Leu Thr Gly Gly Lys
 20 25 30

Phe Arg Gln Glu Ser His Val Glu Phe Ala Thr Gly Glu Leu Leu Thr
 35 40 45

Met Thr Gln Trp Pro Gly Val Trp Ile Pro Met Ala Ser Cys Ser Ser
 50 55 60

Thr Trp Trp Ser Met Ala Leu Ser Pro Asp Ser Leu Ala Asp Ala Asp
 65 70 75 80

Leu Gln Val Gln Asp Phe Glu Glu His Tyr Val Gln Thr Gly Pro Gly
 85 90 95

Gln Leu Phe Val Gly Ser Thr Gln Arg Phe Phe Gln Gly Gly Leu Pro
 100 105 110

109

Ser Phe Leu Arg Cys Asn His Ser Ile Gln Tyr Asn Ala Ala Arg Gly
 115 120 125

~~Pro Gln Pro Gln Leu Val Gln His Leu Arg Ala Ser Ala Ile Ser Ser~~
 130 135 140

Ala Phe Asp Pro Glu Ala Glu Ala Leu Arg Phe Gln Leu Ala Thr Ala
 145 150 155 160

Leu Gln Ala Glu Glu Asn Glu Val Gly Cys Pro Glu Gly Phe Glu Leu
 165 170 175

Asp Ser Gln Gly Ala Phe Cys Val Asp Val Asp Glu Cys Ala Trp Asp
 180 185 190

~~Ala His Leu Cys Arg Glu Gly Gln Arg Cys Val Asn Leu Leu Gly Ser~~
 195 200 205

Tyr Arg Cys Leu Pro Asp Cys Gly Pro Gly Phe Arg Val Ala Asp Gly
 210 215 220

Ala Gly Cys Glu Asp Val Asp Glu Cys Leu Glu Gly Leu Asp Asp Cys
 225 230 235 240

His Tyr Asn Gln Leu Cys Glu Asn Thr Pro Gly Gly His Arg Cys Ser
 245 250 255

Cys Pro Arg Gly Tyr Arg Met Gln Gly Pro Ser Leu Pro Cys Leu Asp
 260 265 270

Val Asn Glu Cys Leu Gln Leu Pro Lys Ala Cys Ala Tyr Gln Cys His
 275 280 285

Asn Leu Gln Gly Ser Tyr Arg Cys Leu Cys Pro Pro Gly Gln Thr Leu
 290 295 300

Leu Arg Asp Gly Lys Ala Cys Thr Ser Leu Glu Arg Asn Gly Gln Asn
 305 310 315 320

Val Thr Thr Val Ser His Arg Gly Pro Leu Leu Pro Trp Leu Arg Pro
 325 330 335

Trp Ala Ser Ile Pro Gly Thr Ser Tyr His Ala Trp Val Ser Leu Arg
 340 345 350

Pro Gly Pro Met Ala Leu Ser Ser Val Gly Arg Ala Trp Cys Pro Pro
 355 360 365

Gly Phe Ile Arg Gln Asn Gly Val Cys Thr Asp Leu Asp Glu Cys Arg
 370 375 380

Val Arg Asn Leu Cys Gln His Ala Cys Arg Asn Thr Glu Gly Ser Tyr
 385 390 395 400

Gln Cys Leu Cys Pro Ala Gly Tyr Arg Leu Leu Pro Ser Gly Lys Asn
 405 410 415

Cys Gln Asp Ile Asn Glu Cys Glu Glu Glu Ser Ile Glu Cys Gly Pro

110

420

425

430

Gly Gln Met Cys Phe Asn Thr Arg Gly Ser Tyr Gln Cys Val Asp Thr
 435 440 445

Pro Cys Pro Ala Thr Tyr Arg Gln Gly Pro Ser Pro Gly Thr Cys Phe
 450 455 460

Arg Arg Cys Ser Gln Asp Cys Gly Thr Gly Gly Pro Ser Thr Leu Gln
 465 470 475 480

Tyr Arg Leu Leu Pro Leu Pro Leu Gly Val Arg Ala His His Asp Val
 485 490 495

Ala Arg Leu Thr Ala Phe Ser Glu Val Gly Val Pro Ala Asn Arg Thr
 500 505 510

Glu Leu Ser Met Leu Glu Pro Asp Pro Arg Ser Pro Phe Ala Leu Arg
 515 520 525

Pro Leu Arg Ala Gly Leu Gly Ala Val Tyr Thr Arg Arg Ala Leu Thr
 530 535 540

Arg Ala Gly Leu Tyr Arg Leu Thr Val Arg Ala Ala Ala Pro Arg His
 545 550 555 560

Gln Ser Val Phe Val Leu Leu Ile Ala Val Ser Pro Tyr Pro Tyr
 565 570 575

<210> 160

<211> 643

<212> PRT

<213> Homo sapiens

<400> 160

Met Gly Glu Pro Asn Arg His Pro Ser Met Phe Leu Leu Leu Leu Val
 1 5 10 15

Leu Glu Arg Leu Tyr Ala Ser Pro Met Asp Gly Thr Ser Ser Ala Leu
 20 25 30

Ser Met Gly Pro Phe Val Pro Phe Ile Met Arg Cys Gly His Ser Pro
 35 40 45

Val Tyr His Ser Arg Glu Met Ala Ala Arg Ala Leu Val Pro Phe Val
 50 55 60

Met Ile Asp His Ile Pro Asn Thr Ile Arg Thr Leu Leu Ser Thr Leu
 65 70 75 80

Pro Ser Cys Thr Asp Gln Cys Phe Arg Gln Asn His Ile His Gly Thr
 85 90 95

Leu Leu Gln Val Phe His Leu Leu Gln Ala Tyr Ser Asp Ser Lys His
 100 105 110

Gly Thr Asn Ser Asp Phe Gln His Glu Leu Thr Asp Ile Thr Val Cys

111

115	120	125
Thr Lys Ala Lys Leu Trp	Leu Ala Lys Arg Gln Asn	Pro Cys Leu Val
130	135	140
Thr Arg Ala Val Tyr	Ile Asp Ile Leu Phe Leu Leu Thr Cys Cys Leu	
145	150	155 160
Asn Arg Ser Ala Lys Asp Asn Gln Pro Val	Leu Glu Ser Leu Gly Phe	
165	170	175
Trp Glu Glu Val Arg Gly Ile Ile Ser Gly Ser Glu Leu Ile Thr Gly		
180	185	190
Phe Pro Trp Ala Phe Lys Val Pro Gly Leu Pro Gln Tyr Leu Gln Ser		
195	200	205
Leu Thr Arg Leu Ala Ile Ala Ala Val Trp Ala Ala Ala Ala Lys Ser		
210	215	220
Gly Glu Arg Glu Thr Asn Val Pro Ile Ser Phe Ser Gln Leu Leu Glu		
225	230	235 240
Ser Ala Phe Pro Glu Val Arg Ser Leu Thr Leu Glu Ala Leu Leu Glu		
245	250	255
Lys Phe Leu Ala Ala Ala Ser Gly Leu Gly Glu Lys Gly Val Pro Pro		
260	265	270
Leu Leu Cys Asn Met Gly Glu Lys Phe Leu Leu Leu Ala Met Lys Glu		
275	280	285
Asn His Pro Glu Cys Phe Cys Lys Ile Leu Lys Ile Leu His Cys Met		
290	295	300
Asp Pro Gly Glu Trp Leu Pro Gln Thr Glu His Cys Val His Leu Thr		
305	310	315 320
Pro Lys Glu Phe Leu Ile Trp Thr Met Asp Ile Ala Ser Asn Glu Arg		
325	330	335
Ser Glu Ile Gln Ser Val Ala Leu Arg Leu Ala Ser Lys Val Ile Ser		
340	345	350
His His Met Gln Thr Cys Val Glu Asn Arg Glu Leu Ile Ala Ala Glu		
355	360	365
Leu Lys Gln Trp Val Gln Leu Val Ile Leu Ser Cys Glu Asp His Leu		
370	375	380
Pro Thr Glu Ser Arg Leu Ala Val Val Glu Val Leu Thr Ser Thr Thr		
385	390	395 400
Pro Leu Phe Leu Thr Asn Pro His Pro Ile Leu Glu Leu Gln Asp Thr		
405	410	415
Leu Ala Leu Trp Lys Cys Val Leu Thr Leu Leu Gln Ser Glu Glu Gln		
420	425	430

112

Ala Val Arg Asp Ala Ala Thr Glu Thr Val Thr Thr Ala Met Ser Gln
 435 440 445

Glu Asn Thr Cys Gln Ser Thr Glu Phe Ala Phe Cys Gln Val Asp Ala
 450 455 460

Ser Ile Ala Leu Ala Leu Ala Leu Ala Val Leu Cys Asp Leu Leu Gln
 465 470 475 480

Gln Trp Asp Gln Leu Ala Pro Gly Leu Pro Ile Leu Leu Gly Trp Leu
 485 490 495

Leu Gly Glu Ser Asp Asp Leu Val Ala Cys Val Glu Ser Met His Gln
 500 505 510

Val Glu Glu Asp Tyr Leu Phe Glu Lys Ala Glu Val Asn Phe Trp Ala
 515 520 525

Glu Thr Leu Ile Phe Val Lys Tyr Leu Cys Lys His Leu Phe Cys Leu
 530 535 540

Leu Ser Lys Ser Gly Trp Arg Pro Pro Ser Pro Glu Met Leu Cys His
 545 550 555 560

Leu Gln Arg Met Val Ser Glu Gln Cys His Leu Leu Ser Gln Phe Phe
 565 570 575

Arg Glu Leu Pro Pro Ala Ala Glu Phe Val Lys Thr Val Glu Phe Thr
 580 585 590

Arg Leu Arg Ile Gln Glu Glu Arg Thr Leu Ala Cys Leu Arg Leu Leu
 595 600 605

Ala Phe Leu Glu Gly Lys Glu Gly Glu Asp Thr Leu Val Leu Ser Val
 610 615 620

Trp Asp Ser Tyr Ala Glu Ser Arg Gln Leu Thr Leu Pro Arg Thr Glu
 625 630 635 640

Ala Ala Cys

<210> 161

<211> 191

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (191)

<223> Xaa equals stop translation

<400> 161

Met Ser Ser Gly Thr Glu Leu Leu Trp Pro Gly Ala Ala Leu Leu Val
 1 5 10 15

113

Leu Leu Gly Val Ala Ala Ser Leu Cys Val Arg Cys Ser Arg Pro Gly
 20 25 30

Ala Lys Arg Ser Glu Lys Ile Tyr Gln Gln Arg Ser Leu Arg Glu Asp
 35 40 45

Gln Gln Ser Phe Thr Gly Ser Arg Thr Tyr Ser Leu Val Gly Gln Ala
 50 55 60

Trp Pro Gly Pro Leu Ala Asp Met Ala Pro Thr Arg Lys Asp Lys Leu
 65 70 75 80

Leu Gln Phe Tyr Pro Ser Leu Glu Asp Pro Ala Ser Ser Arg Tyr Gln
 85 90 95

Asn Phe Ser Lys Gly Ser Arg His Gly Ser Glu Glu Ala Tyr Ile Asp
 100 105 110

Pro Ile Ala Met Glu Tyr Tyr Asn Trp Gly Arg Phe Ser Lys Pro Pro
 115 120 125

Glu Asp Asp Asp Ala Asn Ser Tyr Glu Asn Val Leu Ile Cys Lys Gln
 130 135 140

Lys Thr Thr Glu Thr Gly Ala Gln Gln Glu Gly Ile Gly Gly Leu Cys
 145 150 155 160

Arg Gly Asp Leu Ser Leu Ser Leu Ala Leu Lys Thr Gly Pro Thr Ser
 165 170 175

Gly Leu Cys Pro Ser Ala Ser Pro Glu Glu Asp Glu Gly Ile Xaa
 180 185 190

<210> 162

<211> 64

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (64)

<223> Xaa equals stop translation

<400> 162

Met Lys His Val Leu Asn Leu Tyr Leu Leu Gly Val Val Leu Thr Leu
 1 5 10 15

Leu Ser Ile Phe Val Arg Val Met Glu Ser Leu Glu Gly Leu Leu Glu
 20 25 30

Ser Pro Ser Pro Gly Thr Ser Trp Thr Thr Arg Ser Gln Leu Ala Asn
 35 40 45

Thr Glu Pro Thr Lys Gly Leu Pro Asp His Pro Ser Arg Ser Met Xaa
 50 55 60

114

<210> 163

<211> 118

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (118)

<223> Xaa equals stop translation

<400> 163

Met Ile Phe Leu Thr Val Leu Pro Leu Ala Phe Leu Phe Leu His Ser

1 5 10 15

Gly Phe Tyr His Tyr Ile Ser Phe Ser Cys Leu Phe Ser Leu Ser Leu
20 25 30Ala Leu Phe Phe Phe Leu Asp Val Ala Thr Phe Arg Arg Pro Gly Gln
35 40 45Leu Phe Cys Glu Arg Ser Val Leu Phe Asp Met Phe His Phe Gly Phe
50 55 60Val Ser Leu Phe Leu His Glu Trp Ile Gln Ala Lys His Phe Trp Ala
65 70 75 80Gly Leu Phe Ile Val Leu Pro Ser Asp Val Phe Phe Ser Val His His
85 90 95Leu Glu Ala Pro Asp Gly Ser Phe Pro Asn Ile Ala Lys Leu Ser Leu
100 105 110Ile Ile Leu Leu Arg Xaa
115

<210> 164

<211> 43

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (43)

<223> Xaa equals stop translation

<400> 164

Met Leu Leu Gln Phe Thr Leu Trp Val Phe Gly Ala Ile His Phe Pro

1 5 10 15

Lys Cys Leu Gly Ile Lys Glu Glu Leu Leu Lys Cys Cys Leu Gln Leu
20 25 30Pro Pro Ser Ser Thr Tyr Glu Lys Val Val Xaa
35 40

115

<210> 165

<211> 48

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (48)

<223> Xaa equals stop translation

<400> 165

Met Leu Ser Arg Arg Leu His Cys Leu Val Leu Tyr Phe Leu Leu Leu
1 5 10 15

Leu Leu Ser Phe Ile His Thr Leu Ser Val Ser His Ile Cys Ser Ser
20 25 30

Phe Ile Trp Leu Phe Pro Lys Asn Ile Glu Ser Glu Ala Thr Met Xaa
35 40 45

<210> 166

<211> 46

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (46)

<223> Xaa equals stop translation

<400> 166

Met Glu Lys Met Gly Gln Gly Leu Leu Ser Ser Thr Tyr Leu Thr Val
1 5 10 15

Leu His Leu Ile Gln Leu Val Gly Cys Gly Leu Leu Thr Glu Glu Ile
20 25 30

Lys Glu Ser Lys Tyr Leu Ile Lys Thr Leu Gly Ser Gly Xaa
35 40 45

<210> 167

<211> 207

<212> PRT

<213> Homo sapiens

<400> 167

Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn Cys Ile Phe Phe
1 5 10 15

Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile Thr Ala Ile Ser
20 25 30

116

Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile Phe Phe Pro Leu
 35 40 45

Pro Ala Cys Leu Asn Pro Val Leu Tyr Val Phe Phe Asn Pro Lys Phe
 50 55 60

Lys Glu Asp Trp Lys Leu Leu Lys Arg Arg Val Thr Lys Lys Ser Gly
 65 70 75 80

Ser Val Ser Val Ser Ile Ser Ser Gln Gly Gly Cys Leu Glu Gln Asp
 85 90 95

Phe Tyr Tyr Asp Cys Gly Met Tyr Ser His Leu Gln Gly Asn Leu Thr
 100 105 110

Val Cys Asp Cys Cys Glu Ser Phe Leu Leu Thr Lys Pro Val Ser Cys
 115 120 125

Lys His Leu Ile Lys Ser His Ser Cys Pro Ala Leu Ala Val Ala Ser
 130 135 140

Cys Gln Arg Pro Glu Gly Tyr Trp Ser Asp Cys Gly Thr Gln Ser Ala
 145 150 155 160

His Ser Asp Tyr Ala Asp Glu Glu Asp Ser Phe Val Ser Asp Ser Ser
 165 170 175

Asp Gln Val Gln Ala Cys Gly Arg Ala Cys Phe Tyr Gln Ser Arg Gly
 180 185 190

Phe Pro Leu Val Arg Tyr Ala Tyr Asn Leu Pro Arg Val Lys Asp
 195 200 205

<210> 168
 <211> 51
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (51)
 <223> Xaa equals stop translation

<400> 168
 Met Tyr Ile Phe Glu Leu Ser Leu Tyr Leu Glu Gly Thr Ser Phe Val
 1 5 10 15

Val Val Leu Leu Phe Leu Leu Ile Ser Val Ser Leu Asp Ser Pro Pro
 20 25 30

Thr Thr Lys Gly Trp Asp Ser Val Leu His Ile Trp Val Pro Leu Ile
 35 40 45

Val Gln Xaa
 50

117

<210> 169

<211> 43

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (43)

<223> Xaa equals stop translation

<400> 169

Met Ala His Pro Gly Leu Pro Lys Thr Val Pro Val Tyr Ala Val Val
1 5 10 15

Leu Ala Leu Leu Ile Met Thr Leu Pro Leu Thr Leu Thr Ile Asn Leu
20 25 30

Asp Asp Asn Leu Tyr Gly Asn Ser Ala Lys Xaa
35 40

<210> 170

<211> 56

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (56)

<223> Xaa equals stop translation

<400> 170

Met Arg Pro Trp Trp Ser Leu Leu Leu Glu Ala Cys Ala Thr Cys Ala
1 5 10 15

Gln Thr Gly Pro Thr Arg Ser Thr Ser Cys Thr Gln Glu Val Ser His
20 25 30

Ser Ser Ser Thr Ala Tyr Pro Ala Pro Met Arg Arg Arg Cys Cys Leu
35 40 45

Pro Ser Pro Arg Ser Cys Thr Xaa
50 55

<210> 171

<211> 109

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (109)

<223> Xaa equals stop translation

<400> 171

Met Ala Leu Ala Gly Ser Val Phe Val Leu Gly Gly Val Leu Val Leu

118

1 5 10 15

Cys Val Glu Arg Asn Gly Glu Gly Glu Met Gly Trp Pro Gln His Leu
20 25 30

Pro Lys Ser Gln Pro Leu Ser Pro Pro Val Ala Val Arg Arg Cys Ser
35 40 45

Phe Glu Arg Ser Trp Ile Asp Leu Leu Val Glu Thr Ser Ser Ser Met
50 55 60

Val Thr Cys Arg Gln Gln Val Gly Thr Pro Asn Gly Met Glu Gly Arg
65 70 75 80

Gly Gly Gly Pro Lys Thr Thr Phe Pro Ile Arg Leu Gln Leu Ser Gly
85 90 95

Ala Cys Ala Val Arg Pro Glu Ile Gln Trp Glu Val Xaa
100 105

<210> 172

<211> 51

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (17)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (51)

<223> Xaa equals stop translation

<400> 172

Met Phe Leu Phe Phe Tyr Leu Ser Leu Ala Val Tyr Ala Gln Arg Gln
1 5 10 15

Xaa Ser Gly Ser Cys Arg Gln Thr Asp His Arg Trp Lys Ser Arg Gly
20 25 30

Ala Arg Arg Cys Phe Leu Glu Pro Arg Asp Pro Gly Ser Val Pro Gly
35 40 45

His Pro Xaa
50

<210> 173

<211> 566

<212> PRT

<213> Homo sapiens

<400> 173

Met Ala Pro Leu Ala Leu His Leu Leu Val Leu Val Pro Ile Leu Leu
1 5 10 15

120

Thr Ala Ser Gly Pro Ala Val Lys Arg Ile Thr Phe Ser Pro Pro Leu
 325 330 335

Pro Arg His Met Gln Glu Ala Leu Arg Arg Leu His Tyr Val Pro Ala
 340 345 350

Thr Lys Val Phe Leu Ser Phe Arg Arg Pro Phe Trp Arg Glu Glu His
 355 360 365

Ile Glu Gly Gly His Ser Asn Thr Asp Arg Pro Ser Arg Met Ile Phe
 370 375 380

Tyr Pro Pro Pro Arg Glu Gly Ala Leu Leu Leu Ala Ser Tyr Thr Trp
 385 390 395 400

Ser Asp Ala Ala Ala Ala Phe Ala Gly Leu Ser Arg Glu Glu Ala Leu
 405 410 415

Arg Leu Ala Leu Asp Asp Val Ala Ala Leu His Gly Pro Val Val Arg
 420 425 430

Gln Leu Trp Asp Gly Thr Gly Val Val Lys Arg Trp Ala Glu Asp Gln
 435 440 445

His Ser Gln Gly Gly Phe Val Val Gln Pro Pro Ala Leu Trp Gln Thr
 450 455 460

Glu Lys Asp Asp Trp Thr Val Pro Tyr Gly Arg Ile Tyr Phe Ala Gly
 465 470 475 480

Glu His Thr Ala Tyr Pro His Gly Trp Val Glu Thr Ala Val Lys Leu
 485 490 495

Leu Arg Ala Ala Ile Lys Ile Asn Ser Arg Lys Gly Pro Ala Ser Asp
 500 505 510

Thr Ala Ser Pro Glu Gly His Ala Ser Asp Met Glu Gly Gln Gly His
 515 520 525

Val His Gly Val Ala Ser Ser Pro Ser His Asp Leu Ala Lys Glu Glu
 530 535 540

Gly Ser His Pro Pro Val Gln Gly Gln Leu Ser Leu Gln Asn Thr Thr
 545 550 555 560

His Thr Arg Thr Ser His
 565

<210> 174

<211> 224

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (76)

<223> Xaa equals any of the naturally occurring L-amino acids

121

<400> 174

Met Ala Arg Ala Arg Gly Ser Pro Cys Pro Pro Leu Pro Pro Gly Arg
 1 5 10 15

Met Ser Trp Pro His Gly Ala Leu Leu Phe Leu Trp Leu Phe Ser Pro
 20 25 30

Pro Leu Gly Ala Gly Gly Gly Gly Val Ala Val Thr Ser Ala Ala Gly
 35 40 45

Gly Gly Ser Pro Pro Ala Thr Ser Cys Pro Val Ala Cys Ser Cys Ser
 50 55 60

Asn Gln Ala Ser Arg Val Ile Cys Thr Arg Arg Xaa Leu Ala Glu Val
 65 70 75 80

Pro Ala Ser Ile Pro Val Asn Thr Arg Tyr Leu Asn Leu Gln Glu Asn
 85 90 95

Gly Ile Gln Val Ile Arg Thr Asp Thr Phe Lys His Leu Arg His Leu
 100 105 110

Glu Ile Leu Gln Leu Ser Lys Asn Leu Val Arg Lys Ile Glu Val Gly
 115 120 125

Ala Phe Asn Gly Leu Pro Ser Leu Asn Thr Leu Glu Leu Phe Asp Asn
 130 135 140

Arg Leu Thr Thr Val Pro Thr Gln Ala Phe Glu Tyr Leu Ser Lys Leu
 145 150 155 160

Arg Glu Leu Trp Leu Arg Asn Asn Pro Ile Glu Ser Ile Pro Ser Tyr
 165 170 175

Ala Phe Asn Arg Val Pro Ser Leu Arg Arg Leu Asp Leu Gly Glu Leu
 180 185 190

Lys Arg Leu Glu Tyr Ile Ser Glu Ala Ala Phe Glu Gly Leu Val Asn
 195 200 205

Leu Arg Tyr Leu Asn Leu Gly Met Cys Asn Leu Lys Asp Ile Pro Asn
 210 215 220

<210> 175

<211> 123

<212> PRT

<213> Homo sapiens

<400> 175

Met His Asp Gly Ser Lys Pro Phe Pro Arg Tyr Gly Tyr Lys Pro Ser
 1 5 10 15

Pro Pro Asn Gly Cys Gly Ser Pro Leu Phe Gly Val His Leu Asn Ile

122

20

25

30

Gly Ile Pro Ser Leu Thr Lys Cys Cys Asn Gln His Asp Arg Cys Tyr
 35 40 45

Glu Thr Cys Gly Lys Ser Lys Asn Asp Cys Asp Glu Glu Phe Gln Tyr
 50 55 60

Cys Leu Ser Lys Ile Cys Arg Asp Val Gln Lys Thr Leu Gly Leu Thr
 65 70 75 80

Gln His Val Gln Ala Cys Glu Thr Thr Val Glu Leu Leu Phe Asp Ser
 85 90 95

Val Ile His Leu Gly Cys Lys Pro Tyr Leu Asp Ser Gln Arg Ala Ala
 100 105 110

Cys Arg Cys His Tyr Glu Glu Lys Thr Asp Leu
 115 120

<210> 176

<211> 60

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (60)

<223> Xaa equals stop translation

<400> 176

Met Gly Leu Ser Val Leu Leu Pro Leu Cys Leu Leu Gly Pro Gly Arg
 1 5 10 15

Phe Thr Ser Gly Gln Lys Pro Leu Asp Thr Pro Gly Leu Gly Ala Ala
 20 25 30

Val Leu Ser Val Arg Lys Ala Gly Leu Lys Met Arg Ser His Leu Thr
 35 40 45

Pro Ser Val Cys Thr Val Pro Ser Pro Gly Ser Xaa
 50 55 60

<210> 177

<211> 105

<212> PRT

<213> Homo sapiens

<400> 177

Met Asp Thr Val Phe Leu Ile Gln Tyr Leu Phe Leu Thr Phe Pro Arg
 1 5 10 15

Ile Val Phe Met Leu Gly Phe Val Val Val Leu Ser Phe Leu Leu Gly
 20 25 30

Gly Tyr Leu Leu Phe Val Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr

123

35

40

45

Asn Glu Trp Tyr Arg Gly Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu
 50 55 60

Val Ala Trp Pro Pro Ser Ala Glu Pro Gln Val His Arg Asn Ile His
 65 70 75 80

Ser His Gly Leu Arg Ser Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe
 85 90 95

Pro Cys His Glu Arg Lys Lys Gln Glu
 100 105

<210> 178

<211> 88

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (88)

<223> Xaa equals stop translation

<400> 178

Met Ala Asp Pro His Val Ser Phe Leu Ser Phe Arg Gln Leu Phe Ser
 1 5 10 15

Trp Ala Ala Val Ile Leu Leu Arg Gly Ile Leu Gly Thr Val Ala Pro
 20 25 30

Pro Pro Cys Pro Cys Val Leu Asp Leu Ala Val Tyr Pro Leu His Leu
 35 40 45

Pro Val Glu Ala Pro Cys Leu Glu Val Val Phe Lys Gln Lys Asn Gly
 50 55 60

Lys Asp Asn Cys Leu Val Phe Tyr Pro Asp Pro Ile Pro Leu Arg Gly
 65 70 75 80

Ser Leu Leu Gly Pro Phe Ile Xaa
 85

<210> 179

<211> 88

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (55)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (66)

124

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (88)

<223> Xaa equals stop translation

<400> 179

Met	Ala	Asp	Pro	His	Val	Ser	Phe	Leu	Ser	Phe	Arg	Gln	Leu	Phe	Ser
1				5				10					15		

Trp	Ala	Ala	Val	Ile	Leu	Leu	Arg	Gly	Ile	Leu	Gly	Thr	Val	Ala	Pro
			20				25					30			

Pro	Pro	Cys	Pro	Cys	Val	Leu	Asp	Leu	Ala	Val	Tyr	Pro	Leu	His	Leu
		35					40						45		

Pro	Val	Glu	Ala	Pro	Cys	Xaa	Glu	Val	Val	Phe	Lys	Gln	Lys	Asn	Gly
	50					55					60				

Lys	Xaa	Asn	Cys	Leu	Val	Phe	Tyr	Pro	Asp	Pro	Ile	Pro	Leu	Arg	Gly
65					70					75					80

Ser	Leu	Leu	Gly	Pro	Phe	Ile	Xaa
							85

<210> 180

<211> 49

<212> PRT

<213> Homo sapiens

<400> 180

Met	Asn	Leu	Leu	Gly	Met	Ile	Phe	Ser	Met	Cys	Gly	Leu	Met	Leu	Lys
1				5					10				15		

Leu	Lys	Trp	Cys	Ala	Trp	Val	Ala	Val	Tyr	Cys	Ser	Phe	Ile	Ser	Phe
			20					25					30		

Ala	Asn	Ser	Arg	Ser	Ser	Glu	Asp	Thr	Lys	Gln	Met	Met	Ser	Ser	Phe
			35				40					45			

Met

<210> 181

<211> 23

<212> PRT

<213> Homo sapiens

<400> 181

Leu	Gly	Ser	Leu	Ser	Thr	Ala	Pro	Ser	Ser	Ala	Leu	Pro	Thr	Leu	Gly
1				5					10					15	

Ala	Arg	Arg	Thr	Arg	Ser	Lys
						20

125

<210> 182

<211> 104

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (104)

<223> Xaa equals stop translation

<400> 182

Met Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe
 1 5 10 15

Leu Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile
 20 25 30

Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe
 35 40 45

Ser Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp
 50 55 60

Val Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn
 65 70 75 80

Tyr Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg
 85 90 95

Thr Arg Val Leu Phe Ile Tyr Xaa
 100

<210> 183

<211> 198

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (29)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 183

Met Lys Lys Ser Leu Glu Asn Leu Asn Arg Leu Gln Val Met Leu Leu
 1 5 10 15

His Leu Thr Ala Ala Phe Leu Gln Arg Ala Gln His Xaa Phe Asp Tyr
 20 25 30

Lys Asp Glu Ser Gly Phe Pro Lys Pro Pro Ser Tyr Asn Val Ala Thr
 35 40 45

Thr Leu Pro Ser Tyr Asp Glu Ala Glu Arg Thr Lys Ala Glu Ala Thr
 50 55 60

Ile Pro Leu Val Pro Gly Arg Asp Glu Asp Phe Val Gly Arg Asp Asp

126

65

70

75

80

Phe Asp Asp Ala Asp Gln Leu Arg Ile Gly Asn Asp Gly Ile Phe Met
 85 90 95

Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe Leu
 100 105 110

Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile Ser
 115 120 125

Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe Ser
 130 135 140

Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp Val
 145 150 155 160

Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn Tyr
 165 170 175

Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg Thr
 180 185 190

Arg Val Leu Phe Ile Tyr
 195

<210> 184

<211> 70

<212> PRT

<213> Homo sapiens

<400> 184

Met Leu Leu His Leu Thr Ala Ala Phe Leu Gln Arg Ala Gln Phe Ser
 1 5 10 15

Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp Val
 20 25 30

Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn Tyr
 35 40 45

Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg Thr
 50 55 60

Arg Val Leu Phe Ile Tyr
 65 70

<210> 185

<211> 82

<212> PRT

<213> Homo sapiens

<400> 185

Met Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe
 1 5 10 15

127

Leu Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile
 20 25 30

Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe
 35 40 45

Ser Thr Tyr Phe Pro Ala Phe Met Asn Ser Leu Ser Arg Ser Lys Arg
 50 55 60

Thr Pro Ala Gly Ser Glu Ser Arg Cys Arg Thr Gln Arg Asn Asn His
 65 70 75 80

Leu Leu

<210> 186

<211> 45

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (28)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 186

Met Lys Lys Ser Leu Glu Asn Leu Asn Arg Leu Gln Val Met Leu Leu
 1 5 10 15

His Leu Thr Ala Ala Phe Leu Gln Arg Ala His Xaa Ile Leu Thr Thr
 20 25 30

Arg Met Ser Leu Gly Phe Gln Ser Pro His Leu Thr Met
 35 40 45

<210> 187

<211> 34

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (34)

<223> Xaa equals stop translation

<400> 187

Met Thr Val Met Asp Pro Lys Gln Met Asn Val Ala Ala Ala Val Trp
 1 5 10 15

Ala Val Val Ser Tyr Val Val Ala Asp Met Glu Glu Met Leu Pro Arg
 20 25 30

Ser Xaa

128

<210> 188

<211> 232

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (232)

<223> Xaa equals stop translation

<400> 188

Met Ala Thr Leu Trp Gly Gly Leu Leu Arg Leu Gly Ser Leu Leu Ser
 1 5 10 15

Leu Ser Cys Leu Ala Leu Ser Val Leu Leu Leu Ala His Cys Gln Thr
 20 25 30

Pro Pro Arg Ile Ser Arg Met Ser Asp Val Asn Val Ser Ala Leu Pro
 35 40 45

Ile Lys Lys Asn Ser Gly His Ile Tyr Asn Lys Asn Ile Ser Gln Lys
 50 55 60

Asp Cys Asp Cys Leu His Val Val Glu Pro Met Pro Val Arg Gly Pro
 65 70 75 80

Asp Val Glu Ala Tyr Cys Leu Arg Cys Glu Cys Lys Tyr Glu Glu Arg
 85 90 95

Ser Ser Val Thr Ile Lys Val Thr Ile Ile Ile Tyr Leu Ser Ile Leu
 100 105 110

Gly Leu Leu Leu Leu Tyr Met Val Tyr Leu Thr Leu Val Glu Pro Ile
 115 120 125

Leu Lys Arg Arg Leu Phe Gly His Ala Gln Leu Ile Gln Ser Asp Asp
 130 135 140

Asp Ile Gly Asp His Gln Pro Phe Ala Asn Ala His Asp Val Leu Ala
 145 150 155 160

Arg Ser Arg Ser Arg Ala Asn Val Leu Asn Lys Val Glu Tyr Gly Thr
 165 170 175

Ala Ala Leu Glu Ala Ser Ser Pro Arg Ala Ala Lys Ser Leu Ser Leu
 180 185 190

Thr Gly Met Leu Ser Ser Ala Asn Trp Gly Ile Glu Phe Lys Val Thr
 195 200 205

Arg Lys Lys Gln Ala Asp Asn Trp Lys Gly Thr Asp Trp Val Leu Leu
 210 215 220

Gly Phe Ile Leu Ile Pro Cys Xaa
 225 230

<210> 189

129

<211> 457
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (457)
 <223> Xaa equals stop translation

<400> 189

Met Ala Ala Ala Gly Arg Leu Pro Ser Ser Trp Ala Leu Phe Ser Pro
 1 5 10 15

Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
 20 25 30

Ala Leu His Asn Val Thr Ala Glu Leu Phe Gly Ala Glu Ala Trp Gly
 35 40 45

Thr Leu Ala Ala Phe Gly Asp Leu Asn Ser Asp Lys Gln Thr Asp Leu
 50 55 60

Phe Val Leu Arg Glu Arg Asn Asp Leu Ile Val Phe Leu Ala Asp Gln
 65 70 75 80

Asn Ala Pro Tyr Phe Lys Pro Lys Val Lys Val Ser Phe Lys Asn His
 85 90 95

Ser Ala Leu Ile Thr Ser Val Val Pro Gly Asp Tyr Asp Gly Asp Ser
 100 105 110

Gln Met Asp Val Leu Leu Thr Tyr Leu Pro Lys Asn Tyr Ala Lys Ser
 115 120 125

Glu Leu Gly Ala Val Ile Phe Trp Gly Gln Asn Gln Thr Leu Asp Pro
 130 135 140

Asn Asn Met Thr Ile Leu Asn Arg Thr Phe Gln Asp Glu Pro Leu Ile
 145 150 155 160

Met Asp Phe Asn Gly Asp Leu Ile Pro Asp Ile Phe Gly Ile Thr Asn
 165 170 175

Glu Ser Asn Gln Pro Gln Ile Leu Leu Gly Gly Asn Leu Ser Trp His
 180 185 190

Pro Ala Leu Thr Thr Thr Ser Lys Met Arg Ile Pro His Ser His Ala
 195 200 205

Phe Ile Asp Leu Thr Glu Asp Phe Thr Ala Asp Leu Phe Leu Thr Thr
 210 215 220

Leu Asn Ala Thr Thr Ser Thr Phe Gln Phe Glu Ile Trp Glu Asn Leu
 225 230 235 240

Asp Gly Asn Phe Ser Val Ser Thr Ile Leu Glu Lys Pro Gln Asn Met
 245 250 255

130

Met Val Val Gly Gln Ser Ala Phe Ala Asp Phe Asp Gly Asp Gly His
260 265 270

Met Asp His Leu Leu Pro Gly Cys Glu Asp Lys Asn Cys Gln Lys Ser
275 280 285

Thr Ile Tyr Leu Val Arg Ser Gly Met Lys Gln Trp Val Pro Val Leu
290 295 300

Gln Asp Phe Ser Asn Lys Gly Thr Leu Trp Gly Phe Val Pro Phe Val
305 310 315 320

Asp Glu Gln Gln Pro Thr Glu Ile Pro Ile Pro Ile Thr Leu His Ile
325 330 335

Gly Asp Tyr Asn Met Asp Gly Tyr Pro Asp Ala Leu Val Ile Leu Lys
340 345 350

Asn Thr Ser Gly Ser Asn Gln Gln Ala Phe Leu Leu Glu Asn Val Pro
355 360 365

Cys Asn Asn Ala Ser Cys Glu Glu Ala Arg Arg Met Phe Lys Val Tyr
370 375 380

Trp Glu Leu Thr Asp Leu Asn Gln Ile Lys Asp Ala Met Val Ala Thr
385 390 395 400

Phe Phe Asp Ile Tyr Glu Asp Gly Ile Leu Asp Ile Val Val Leu Ser
405 410 415

Lys Gly Tyr Thr Lys Asn Asp Phe Ala Ile His Thr Leu Lys Asn Asn
420 425 430

Phe Glu Ala Asp Ala Tyr Phe Val Lys Val Ile Val Leu Ser Gly Leu
435 440 445

Cys Ser Asn Asp Cys Pro Arg Arg Xaa
450 455

<210> 190

<211> 185

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (185)

<223> Xaa equals stop translation

<400> 190

Met Leu Phe Leu Phe Ser Met Ala Thr Leu Leu Arg Thr Ser Phe Ser
1 5 10 15

Asp Pro Gly Val Ile Pro Arg Ala Leu Pro Asp Glu Ala Ala Phe Ile
20 25 30

Glu Met Glu Ile Glu Ala Thr Asn Gly Ala Val Pro Gln Gly Gln Arg

131

35

40

45

Pro Pro Pro Arg Ile Lys Asn Phe Gln Ile Asn Asn Gln Ile Val Lys
 50 55 60

Leu Lys Tyr Cys Tyr Thr Cys Lys Ile Phe Arg Pro Pro Arg Ala Ser
 65 70 75 80

His Cys Ser Ile Cys Asp Asn Cys Val Glu Arg Phe Asp His His Cys
 85 90 95

Pro Trp Val Gly Asn Cys Val Gly Lys Arg Asn Tyr Arg Tyr Phe Tyr
 100 105 110

Leu Phe Ile Leu Ser Leu Ser Leu Leu Thr Ile Tyr Val Phe Ala Phe
 115 120 125

Asn Ile Val Tyr Val Ala Leu Lys Ser Leu Lys Ile Gly Phe Leu Glu
 130 135 140

Thr Leu Lys Gly Asn Ser Trp Asn Cys Ser Arg Ser Pro His Leu Leu
 145 150 155 160

Leu Tyr Thr Leu Val Arg Arg Gly Thr Asp Trp Ile Ser Tyr Phe Pro
 165 170 175

Arg Gly Ser Gln Pro Asp Asn Gln Xaa
 180 185

<210> 191

<211> 147

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (147)

<223> Xaa equals stop translation

<400> 191

Met Arg Val Leu Val Val Thr Ile Ala Pro Ile Tyr Trp Ala Leu Ala
 1 5 10 15

Arg Glu Ser Gly Glu Ala Leu Asn Gly His Ser Leu Thr Gly Gly Lys
 20 25 30

Phe Arg Gln Ser His Thr Trp Ser Leu Leu Gln Gly Ala Ala His Asp
 35 40 45

Asp Pro Val Ala Arg Gly Leu Asp Pro Asp Gly Leu Leu Leu Asp
 50 55 60

Val Val Val Asn Gly Val Val Pro Gly Arg Ala Trp Leu Thr Gln Ile
 65 70 75 80

Phe Lys Cys Arg Thr Leu Lys Lys His Tyr Val Gln Thr Arg Ala Trp
 85 90 95

132

Pro Ala Val Arg Gly Leu His Thr Ala Leu Leu Pro Gly Arg Pro Pro
 100 105 110

Leu Val Pro Thr Leu Gln Pro Gln His Pro Val Gln Arg Gly Pro Gly
 115 120 125

Pro Pro Ala Pro Ala Gly Ala Ala Pro Ala Gly Leu Ser Tyr Gln Leu
 130 135 140

Gly Leu Xaa
 145

<210> 192
 <211> 125
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (125)
 <223> Xaa equals stop translation

<400> 192
 Met Gly Glu Pro Asn Arg His Pro Ser Met Phe Leu Leu Leu Val
 1 5 10 15

Leu Glu Arg Leu Tyr Ala Ser Pro Met Asp Gly Thr Ser Ser Ala Leu
 20 25 30

Ser Met Gly Pro Phe Val Pro Phe Ile Met Arg Cys Gly His Ser Pro
 35 40 45

Val Tyr His Ser Arg Glu Met Ala Ala Arg Ala Leu Val Pro Phe Val
 50 55 60

Met Ile Asp His Ile Pro Asn Thr Ile Arg Thr Leu Leu Ser Thr Leu
 65 70 75 80

Pro Ser Cys Thr Asp Gln Cys Phe Arg Ala Lys Pro His Ser Trp Gly
 85 90 95

His Phe Ser Arg Phe Phe His Leu Leu Gln Ala Tyr Ser Asp Ser Lys
 100 105 110

Thr Arg Asn Glu Phe Arg Leu Pro Ala Arg Ala Asp Xaa
 115 120 125

<210> 193
 <211> 52
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (52)

133

<223> Xaa equals stop translation

~~<400> 193~~

Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn Cys Ile Phe Phe
 1 5 10 15

Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile Thr Ala Ile Ser
 20 25 30

Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile Phe Phe Pro Cys
 35 40 45

Leu Leu Ala Xaa
 50

<210> 194

<211> 320

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (68)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (115)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (213)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (320)

<223> Xaa equals stop translation

<400> 194

Met Ala Pro Leu Ala Leu His Leu Leu Val Leu Val Pro Ile Leu Leu
 1 5 10 15

Ser Leu Val Ala Ser Gln Asp Trp Lys Ala Glu Arg Ser Gln Asp Pro
 20 25 30

Phe Glu Lys Cys Met Gln Asp Pro Asp Tyr Glu Gln Leu Leu Lys Val
 35 40 45

Thr Ile Leu Glu Ala Asp Asn Arg Ile Gly Gly Arg Ile Phe Thr Tyr
 50 55 60

Arg Asp Gln Xaa Thr Gly Trp Ile Gly Glu Leu Gly Ala Met Arg Met
 65 70 75 80

Pro Ser Ser His Arg Ile Leu His Lys Leu Cys Gln Gly Leu Gly Leu

```
<220>
<221> SITE
<222> (38)
<223> Xaa equals any of the naturally occurring L-amino acids
```

135

<220>

<221> SITE

<222> (53)

<223> Xaa equals any of the naturally occurring-L-amino-acids

<400> 195

Pro Phe Cys Ser Gly Phe Phe Pro Ser Leu Trp Ile Tyr Leu Pro Phe
 1 5 10 15

Ile Phe Asn Val Ser Asp Leu Trp Met Gly Ser Leu Ser Gly Cys Ala
 20 25 30

Leu Pro Phe Cys Leu Xaa Val Phe Phe Leu Thr Val Ser Pro Ser Ala
 35 40 45

Val Gly Leu Leu Xaa Phe Ala Gly Gly Pro Leu Gln Thr Leu Phe Ala
 50 55 60

Trp Val Ser Pro Val Glu Ala Ala Glu Gln Gln Arg Leu Leu Pro Val
 65 70 75 80

Leu Ser Ser Gly Ser Phe Val Ser Glu Gly Thr Cys Gln Met Pro Ala
 85 90 95

Arg Ala Leu Leu Tyr Glu Val Ser Val Gly Pro Tyr Trp Glu Ile Pro
 100 105 110

Pro Ser Gln Asp Thr Arg Arg Ser Gly Thr Tyr Leu Arg Arg Gln Ser
 115 120 125

Asp Pro
 130

<210> 196

<211> 108

<212> PRT

<213> Homo sapiens

<400> 196

His Glu Gly Ser Cys Arg Ala Pro Gly Phe Ser Ala His Lys Gly Arg
 1 5 10 15

Gly Cys Pro Ser Pro Arg Met Thr Leu Pro Ser Arg Ala Leu Ala Ser
 20 25 30

Leu Gly Val Gly Val Trp Gly Met Leu Arg Leu Asn Gln Val Thr Val
 35 40 45

Ser Cys Gly Gly Ser Arg Trp Ser Ser Arg Val Ala Leu Gly Ala Phe
 50 55 60

Ser Trp Val Cys Gly Val Ala Leu Val Leu Gln Pro Ser Gly Gly Gly
 65 70 75 80

Leu Gly Leu Thr Ser Pro Ser Glu Gly Cys Trp Glu Gly Glu Leu Ala
 85 90 95

136

Leu Ala Val Leu Arg Ala Pro Gly Gly Ser Pro Ser
 100 105

<210> 197
 <211> 104
 <212> PRT
 <213> Homo sapiens

<400> 197
 Ile Pro Leu Thr Leu Pro Gly Ile Phe Leu Leu Ile Arg Leu Phe Trp
 1 5 10 15
 Arg Leu Gly Gln Ser Ile Cys Gly Pro Gly Lys Leu Val Leu Trp Pro
 20 25 30
 Gln Phe Cys Cys Gly Cys Ala Val Ile Ser Gly His Cys Val Pro Arg
 35 40 45
 Gly Met Pro Ser Ser Trp Leu Pro Gly Cys Phe Val Leu Leu Cys Leu
 50 55 60
 Val Ala Val Gly Cys Gln Leu Arg Glu Trp Gly Val Gly Gly Val Ser
 65 70 75 80
 Ala Val Gly Leu Leu Ala Leu Pro His Leu Gln Val Leu Gly Met Arg
 85 90 95
 Gly Arg Gly Leu Ile Ser Gly Gly
 100

<210> 198
 <211> 237
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (142)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 198
 Gly Pro Ala Gly Lys Glu Ala Trp Ile Trp Ser Trp Leu Leu Pro Ser
 1 5 10 15
 Pro Gly Pro Ala Pro Leu Pro Ser Ala Ser Trp Gly Leu Cys Gly Asp
 20 25 30
 Ala Pro Arg Ala Ala Ala Arg Gly Pro Val Glu Pro Gly Ala Ala Arg
 35 40 45
 Met Ala Leu Leu Ser Arg Pro Ala Leu Thr Leu Leu Leu Leu Met
 50 55 60
 Ala Ala Val Val Arg Cys Gln Glu Gln Ala Gln Thr Thr Asp Trp Arg
 65 70 75 80

137

Ala Thr Leu Lys Thr Ile Arg Asn Gly Val His Lys Ile Asp Thr Tyr
85 90 95

Leu Asn Ala Ala Leu Asp Leu Leu Gly Gly Glu Asp Gly Leu Cys Gln
100 105 110

Tyr Lys Cys Ser Asp Gly Ser Lys Pro Phe Pro Arg Tyr Gly Tyr Lys
115 120 125

Pro Ser Pro Pro Asn Gly Cys Gly Ser Pro Leu Phe Gly Xaa His Leu
130 135 140

Asn Ile Gly Ile Pro Ser Leu Thr Lys Cys Cys Asn Gln His Asp Arg
145 150 155 160

Cys Tyr Glu Thr Cys Gly Lys Ser Lys Asn Asp Cys Asp Glu Glu Phe
165 170 175

Gln Tyr Cys Leu Ser Lys Ile Cys Arg Asp Val Gln Lys Thr Leu Gly
180 185 190

Leu Thr Gln His Val Gln Ala Cys Glu Thr Thr Val Glu Leu Leu Phe
195 200 205

Asp Ser Val Ile His Leu Gly Cys Lys Pro Tyr Leu Asp Ser Gln Arg
210 215 220

Ala Ala Cys Arg Cys His Tyr Glu Glu Lys Thr Asp Leu
225 230 235

<210> 199

<211> 8

<212> PRT

<213> Homo sapiens

<400> 199

Cys Cys Asn Gln His Asp Arg Cys

1

5

<210> 200

<211> 15

<212> PRT

<213> Homo sapiens

<400> 200

Ser Leu Thr Lys Cys Cys Asn Gln His Asp Arg Cys Tyr Glu Thr

1

5

10

15

<210> 201

<211> 16

<212> PRT

<213> Homo sapiens

<400> 201

Leu Thr Lys Cys Cys Asn Gln His Asp Arg Cys Tyr Glu Thr Cys Gly

138

1

5

10

15

<210> 202

<211> 260

<212> PRT

<213> Homo sapiens

<400> 202

Gly Thr Ser Ser Ala Arg Pro Arg Gly Ala Leu Pro Gly Gly Ser Ala
 1 5 10 15

Pro Ser Ala Pro His Gly Gln Leu Pro Gly Arg Ala Gln Pro Ala Pro
 20 25 30

Val Ser Gly Pro Pro Pro Thr Ser Gly Leu Cys His Phe Asp Pro Ala
 35 40 45

Ala Pro Trp Pro Leu Trp Pro Gly Pro Trp Gln Leu Pro Pro His Pro
 50 55 60

Gln Asp Trp Pro Ala His Pro Asp Ile Pro Gln Asp Trp Val Ser Phe
 65 70 75 80

Leu Arg Ser Phe Gly Gln Leu Thr Leu Cys Pro Arg Asn Gly Thr Val
 85 90 95

Thr Gly Lys Trp Arg Gly Ser His Val Val Gly Leu Leu Thr Thr Leu
 100 105 110

Asn Phe Gly Asp Gly Pro Asp Arg Asn Lys Thr Arg Thr Phe Gln Ala
 115 120 125

Thr Val Leu Gly Ser Gln Met Gly Leu Lys Gly Ser Ser Ala Gly Gln
 130 135 140

Leu Val Leu Ile Thr Ala Arg Val Thr Thr Glu Arg Thr Ala Gly Thr
 145 150 155 160

Cys Leu Tyr Phe Ser Ala Val Pro Gly Ile Leu Pro Ser Ser Gln Pro
 165 170 175

Pro Ile Ser Cys Ser Glu Glu Gly Ala Gly Asn Ala Thr Leu Ser Pro
 180 185 190

Arg Met Gly Glu Glu Cys Val Ser Val Trp Ser His Glu Gly Leu Val
 195 200 205

Leu Thr Lys Leu Leu Thr Ser Glu Glu Leu Ala Leu Cys Gly Ser Arg
 210 215 220

Leu Leu Val Leu Gly Ser Phe Leu Leu Leu Phe Cys Gly Leu Leu Cys
 225 230 235 240

Cys Val Thr Ala Met Cys Phe His Pro Arg Arg Glu Ser His Trp Ser

139

245

250

255

Arg Thr Arg Leu
260

<210> 203
<211> 80
<212> PRT
<213> Homo sapiens

<400> 203
Ala Arg Ala Pro Pro Gly Pro Glu Gly Leu Ser Pro Glu Ala Gln Pro
1 5 10 15

Pro Leu Leu Pro Met Gly Asn Cys Gln Ala Gly His Asn Leu His Leu
20 25 30

Cys Leu Ala His His Pro Pro Leu Val Cys Ala Thr Leu Ile Leu Leu
35 40 45

Leu Leu Gly Leu Ser Gly Leu Gly Leu Gly Ser Phe Leu Leu Thr His
50 55 60

Arg Thr Gly Leu Arg Thr Leu Thr Ser Pro Arg Thr Gly Ser Leu Phe
65 70 75 80

<210> 204
<211> 224
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (6)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (9)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (22)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (143)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE

140

<222> (186)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 204

Arg Phe Leu Ser Val Xaa Pro Gln Xaa Glu Val Pro Phe Leu Leu His
 1 5 10 15

Pro Cys Val Cys Phe Xaa Gly Gly His Pro Ser Leu Leu Pro Asp Pro
 20 25 30

Cys Arg Ala Val Gly Gly Gly Trp Glu Ala Pro Arg Cys Cys Leu His
 35 40 45

Glu Ala Leu Cys Gln Ser Leu Gly Cys Lys Ala Glu Glu Ile Val Ser
 50 55 60

Val Ser Glu Ser Ser Ser Ala Gln Arg Cys Trp Tyr Leu Leu Arg Gly
 65 70 75 80

Arg Lys Ala Gly Gly Arg Gly Pro Ala Ser Pro Val Leu Phe Ala Leu
 85 90 95

Met Arg Leu Glu Ser Leu Cys His Leu Cys Leu Ala Cys Leu Phe Phe
 100 105 110

Arg Leu Pro Ala Thr Arg Thr Val Tyr Cys Met Asn Glu Ala Glu Ile
 115 120 125

Val Asp Val Ala Leu Gly Ile Leu Ile Glu Ser Arg Lys Gln Xaa Lys
 130 135 140

Ala Cys Glu Gln Pro Ala Leu Ala Gly Ala Asp Asn Pro Glu His Ser
 145 150 155 160

Pro Pro Cys Ser Val Ser Pro His Thr Ser Ser Gly Ser Ser Ser Glu
 165 170 175

Glu Glu Asp Ser Gly Lys Gln Ala Leu Xaa Pro Gly Leu Ser Pro Ser
 180 185 190

Gln Arg Pro Gly Gly Ser Ser Ser Ala Cys Ser Arg Ser Pro Glu Glu
 195 200 205

Glu Glu Glu Glu Asp Val Leu Lys Tyr Val Arg Glu Ile Phe Phe Ser
 210 215 220

<210> 205

<211> 199

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (35)

141

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (103)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (191)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 205

Val Pro Gly Trp Pro Arg Ala Cys Ser Pro Cys Gln Ala Asp Ser Pro

1 5 10 15

Arg Ala His Pro Pro Lys Leu Arg Gly Ile Leu Arg Trp Ala Pro Val
20 25 30Pro Leu Xaa Cys Ala Ala Leu Cys Pro Pro Leu Asp Ser Gly Met Ser
35 40 45Met Ala Ala Cys Pro Glu Ala Pro Glu Pro Ser Phe Leu Arg Glu Val
50 55 60Pro Ser Ser Pro Ala Ser Thr Gln Trp His Arg Pro Cys Asn Phe Arg
65 70 75 80Gln Val Glu Ala Asn Pro Arg Lys Glu Pro Lys Asn Leu Val Trp Arg
85 90 95Asp Val Ser Leu Gly Gln Xaa Ser Arg Thr Pro Arg Gly Ser Gly Leu
100 105 110Glu Leu Val Arg Val Cys Gly Gly Gly Met Gln Arg Asp Lys Thr Val
115 120 125Val Glu Glu Arg Val Gly Glu Glu Arg Glu Arg Glu Arg Glu
130 135 140Ser Leu Gly Gly Ala Gly Lys His Gly Glu Met Arg Cys Val Tyr Val
145 150 155 160Arg Glu Ser Val Gly Ala Pro Gly Arg Ala Gly Gly Gly Gly Asn Gly
165 170 175Val Asn Ser Val Gly Cys Val Arg Thr Val His Ser Gly Ser Xaa Pro
180 185 190Pro Pro Ser Ala Gly Val Ser
195

<210> 206

<211> 174

<212> PRT

<213> Homo sapiens

142

<400> 206

Thr Arg Pro Gly Lys Glu Leu Asn Leu Val Phe Gly Leu Gln Leu Ser
 1 5 10 15

Met Ala Arg Ile Gly Ser Thr Val Asn Met Asn Leu Met Gly Trp Leu
 20 25 30

Tyr Ser Lys Ile Glu Ala Leu Leu Gly Ser Ala Gly His Thr Thr Leu
 35 40 45

Gly Ile Thr Leu Met Ile Gly Gly Ile Thr Cys Ile Leu Ser Leu Ile
 50 55 60

Cys Ala Leu Ala Leu Ala Tyr Leu Asp Gln Arg Ala Glu Arg Ile Leu
 65 70 75 80

His Lys Glu Gln Gly Lys Thr Gly Glu Val Ile Lys Leu Thr Asp Val
 85 90 95

Lys Asp Phe Ser Leu Pro Leu Trp Leu Ile Phe Ile Ile Cys Val Cys
 100 105 110

Tyr Tyr Val Ala Val Phe Pro Phe Ile Gly Leu Gly Lys Val Phe Phe
 115 120 125

Thr Glu Lys Phe Gly Phe Ser Ser Gln Ala Ala Ser Ala Ile Asn Ser
 130 135 140

Val Val Tyr Val Ile Ser Ala Pro Met Ser Pro Val Phe Gly Leu Leu
 145 150 155 160

Val Asp Lys Thr Gly Lys Asn Ile Ile Trp Val Leu Cys Ala
 165 170

<210> 207

<211> 31

<212> PRT

<213> Homo sapiens

<400> 207

Cys Lys Asp Leu Cys Ser Arg Val Tyr Leu Leu Thr Leu Ser Pro Leu
 1 5 10 15

Leu Ser Tyr Asp Pro Ala Thr Ser His Ser Pro Arg Asn Thr Gln
 20 25 30

<210> 208

<211> 369

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (78)

<223> Xaa equals any of the naturally occurring L-amino acids

143

<400> 208

Ile Ile Cys Glu Cys Trp Glu Glu Glu Cys Gln Ser Cys Arg Leu Lys
 1 5 10 15

Ile Thr Gln Pro Arg Glu Ile Cys Arg Met Asp Phe Leu Val Leu Phe
 20 25 30

Leu Phe Tyr Leu Ala Ser Val Leu Met Gly Leu Val Leu Ile Cys Val
 35 40 45

Cys Ser Lys Thr His Ser Leu Lys Gly Leu Ala Arg Gly Gly Ala Gln
 50 55 60

Ile Phe Ser Cys Ile Ile Pro Glu Cys Leu Gln Arg Ala Xaa His Gly
 65 70 75 80

Leu Leu His Tyr Leu Phe His Thr Arg Asn His Thr Phe Ile Val Leu
 85 90 95

His Leu Val Leu Gln Gly Met Val Tyr Thr Glu Tyr Thr Trp Glu Val
 100 105 110

Phe Gly Tyr Cys Gln Glu Leu Glu Leu Ser Leu His Tyr Leu Leu Leu
 115 120 125

Pro Tyr Leu Leu Leu Gly Val Asn Leu Phe Phe Phe Thr Leu Thr Cys
 130 135 140

Gly Thr Asn Pro Gly Ile Ile Thr Lys Ala Asn Glu Leu Leu Phe Leu
 145 150 155 160

His Val Tyr Glu Phe Asp Glu Val Met Phe Pro Lys Asn Val Arg Cys
 165 170 175

Ser Thr Cys Asp Leu Arg Lys Pro Ala Arg Ser Lys His Cys Ser Val
 180 185 190

Cys Asn Trp Cys Val His Arg Phe Asp His His Cys Val Trp Val Asn
 195 200 205

Asn Cys Ile Gly Ala Trp Asn Ile Arg Tyr Phe Leu Ile Tyr Val Leu
 210 215 220

Thr Leu Thr Ala Ser Ala Ala Thr Val Ala Ile Val Ser Thr Thr Phe
 225 230 235 240

Leu Val His Leu Val Val Met Ser Asp Leu Tyr Gln Glu Thr Tyr Ile
 245 250 255

Asp Asp Leu Gly His Leu His Val Met Asp Thr Val Phe Leu Ile Gln
 260 265 270

Tyr Leu Phe Leu Thr Phe Pro Arg Ile Val Phe Met Leu Gly Phe Val
 275 280 285

Val Val Leu Ser Phe Leu Leu Gly Gly Tyr Leu Leu Phe Val Leu Tyr
 290 295 300

WO 00/04140

144

Leu Ala Ala Thr Asn Gln Thr Thr Asn Glu Trp Tyr Arg Gly Asp Trp
 305 310 315 320

Ala Trp Cys Gln Arg Cys Pro Leu Val Ala Trp Pro Pro Ser Ala Glu
 325 330 335

Pro Gln Val His Arg Asn Ile His Ser His Gly Leu Arg Ser Asn Leu
 340 345 350

Gln Glu Ile Phe Leu Pro Ala Phe Pro Cys His Glu Arg Lys Lys Gln
 355 360 365

Glu

<210> 209
 <211> 147
 <212> PRT
 <213> Homo sapiens

<400> 209
 Leu Leu Ser Phe Lys Ile Arg Gly Leu Arg Thr Glu Asp Ala Gly Trp
 1 5 10 15
 Ala Gln Ser Ser Ser Gly Gly Leu Cys Val Arg Gly Asp Ala Phe Trp
 20 25 30
 Met Pro Ser Ser Ser Ser Gly Leu Gly Ser Pro Ser Arg Pro Pro Ser
 35 40 45
 Ser Phe Leu Cys Leu Leu Leu Leu Leu Pro Pro Ala Ala Leu Ala
 50 55 60
 Leu Leu Leu Phe Phe Leu Asp Phe Phe Pro Pro Arg Ala Ala Val Ser
 65 70 75 80
 Pro Phe Leu Pro Asp His Cys Ser Ala Arg Gln Pro Arg Val Trp Arg
 85 90 95
 Arg Glu Thr Leu Asn Arg Ser Ala Ser Gly Leu Gly Cys Trp Ala Arg
 100 105 110
 Ser Thr Glu Gln Gly Ala Val Gly Val Ala Thr Gly Thr Val Leu Asp
 115 120 125
 Ile Ser Leu Pro Ala Ser Cys Leu Ser Leu Trp Pro Pro Gly Pro Ser
 130 135 140
 Gly Gly Ile
 145

<210> 210
 <211> 143
 <212> PRT
 <213> Homo sapiens

WO 00/04140

145

<400> 210

Gln Leu Gly Leu Cys Leu Thr Ser Ala Ser Leu Pro Pro Ala Ser Arg
 1 5 10 15

Cys Gly His Gln Ala Pro Leu Gly Ala Ser Asp Leu Ser Ala His His
 20 25 30

Ser Ala Pro Gly Phe Ser Asp Ser Tyr Phe Thr Met Ser Cys Gln Ser
 35 40 45

Ser Leu Ser Arg Ala Glu Ile Leu Gln Cys Pro Leu Val Pro Ser Val
 50 55 60

Ser Pro Pro Thr His Leu Pro Gln Gly Arg Ala Asn Lys Ser Ser Arg
 65 70 75 80

Ala Ser Leu Pro Leu Leu Pro Gln Thr His Trp Cys Leu Phe Pro Ser
 85 90 95

Ala Arg Gly Trp Arg Arg Gly Ile Gln Ser Gly Leu Pro Pro Gly Gly
 100 105 110

Ser Cys Thr Ser Pro Arg Ser Pro Pro Gln Thr Leu His Gln His Ile
 115 120 125

Thr Leu Val Asn His Asn Thr Ser Tyr Trp Gln Ser Pro Ser Thr
 130 135 140

<210> 211

<211> 160

<212> PRT

<213> Homo sapiens

<400> 211

His Gln Pro Pro Cys Leu Leu Pro Leu Ala Val Ala Thr Arg Pro Leu
 1 5 10 15

Trp Gly His Leu Thr Cys Leu Pro Ile Ile Leu His Leu Val Ser Val
 20 25 30

Thr Leu Thr Ser Pro Cys Leu Ala Asn Gln Ala Phe Gln Gly Gln Arg
 35 40 45

Ser Tyr Asn Ala Leu Trp Cys Pro Leu Phe Leu Leu Leu Pro Thr Ser
 50 55 60

Pro Lys Gly Glu Gln Thr Asn His Pro Glu Pro Ala Cys Pro Cys Phe
 65 70 75 80

Pro Lys Leu Thr Gly Val Phe Ser Leu Gln His Val Val Gly Ala Glu
 85 90 95

Glu Phe Ser Gln Val Phe Leu Leu Val Asp Pro Val Pro Val Leu Asp
 100 105 110

His Leu Leu Lys Leu Phe Thr Ser Thr Ser His Leu Leu Ile Ile Ile
 115 120 125

146

Pro His Ile Gly Lys Ala Pro Ala Pro Asp Ser Leu Leu Glu Glu Leu
 130 135 140

Ser Leu Ser Leu Ala Thr His Cys Lys Val Ala Val Ala Arg Phe Thr
 145 150 155 160

<210> 212

<211> 157

<212> PRT

<213> Homo sapiens

<400> 212

Met Ala Ala Glu Gly Ser Arg Phe Ser Ser Gln Ser Pro Gly Leu Val
 1 5 10 15

Asp Arg Gln Gly Pro Lys Cys Asp Pro Ser Arg Leu Val Ser Pro Trp
 20 25 30

Gly Arg His Gly Leu Arg Ile Leu Gln Ile Gly His His His Gly Arg
 35 40 45

Asp Gly Gln His Glu Ala Thr His His Leu Leu Arg Val Leu Arg Ala
 50 55 60

Pro Arg Val Gly Lys Ala Asp Glu Gly Ala Val Asp Ser Asp Pro Ser
 65 70 75 80

Thr Pro Leu Gln Leu Lys His Glu Ala Ala His Ala Glu Asp His Ala
 85 90 95

Gln Gln Val His Val Val Arg Arg Arg Val Val Gln Gly Arg Val Thr
 100 105 110

Phe Ala Arg Arg Gly Leu Val Pro Gln His Phe Val Arg Pro Pro Trp
 115 120 125

Val Arg His Ile Val Ser Gly His Ser Glu Ser Lys Ala Arg Ser Arg
 130 135 140

Leu Phe Arg Cys Arg Asn Arg Ser Phe Arg Arg Ala Ser
 145 150 155

<210> 213

<211> 38

<212> PRT

<213> Homo sapiens

<400> 213

Arg Leu Val Ser Pro Trp Gly Arg His Gly Leu Arg Ile Leu Gln Ile
 1 5 10 15

Gly His His His Gly Arg Asp Gly Gln His Glu Ala Thr His His Leu

147

20

25

30

Leu-Arg-Val-Leu-Arg-Ala
35

<210> 214
<211> 12
<212> PRT
<213> Homo sapiens

<400> 214
Pro Thr Asp Val Leu Lys Ile Arg Met Gln Ala Gln
1 5 10

<210> 215
<211> 7
<212> PRT
<213> Homo sapiens

<400> 215
Thr Tyr Glu Gln Leu Lys Arg
1 5

<210> 216
<211> 137
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (22)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (33)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (71)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 216
Arg Pro Arg Pro Ser Ala Ser Ser Leu Ala Arg Ser Ala Ser Leu Leu
1 5 10 15

Pro Ala Ala His Gly Xaa Gly Val Gly Gly Ala Gly Gly Gly Ser Ser
20 25 30

Xaa Leu Arg Ser Arg Tyr Gln Gln Leu Gln Asn Glu Glu Glu Ser Gly
35 40 45

Glu Pro Glu Gln Ala Ala Gly Asp Ala Pro Pro Pro Tyr Ser Ser Ile
50 55 60

148

Ser Ala Glu Ser Ala His Xaa Phe Asp Tyr Lys Asp Glu Ser Gly Phe
 65 70 75 80

Pro Lys Pro Pro Ser Tyr Asn Val Ala Thr Thr Leu Pro Ser Tyr Asp
 85 90 95

Glu Ala Glu Arg Thr Lys Ala Glu Ala Thr Ile Pro Leu Val Pro Gly
 100 105 110

Arg Asp Glu Asp Phe Val Gly Arg Asp Asp Phe Asp Asp Ala Asp Gln
 115 120 125

Leu Arg Ile Gly Asn Asp Gly Ile Phe
 130 135

<210> 217

<211> 20

<212> PRT

<213> Homo sapiens

<400> 217

Arg Tyr Gln Gln Leu Gln Asn Glu Glu Glu Ser Gly Glu Pro Glu Gln
 1 5 10 15

Ala Ala Gly Asp
 20

<210> 218

<211> 22

<212> PRT

<213> Homo sapiens

<400> 218

Pro Gly Arg Asp Glu Asp Phe Val Gly Arg Asp Asp Phe Asp Asp Ala
 1 5 10 15

Asp Gln Leu Arg Ile Gly
 20

<210> 219

<211> 103

<212> PRT

<213> Homo sapiens

<400> 219

Met Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe
 1 5 10 15

Leu Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile
 20 25 30

Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe
 35 40 45

149

Ser Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp
 50 55 60

Val Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn
 65 70 75 80

Tyr Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg
 85 90 95

Thr Arg Val Leu Phe Ile Tyr
 100

<210> 220

<211> 198

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (29)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 220

Met Lys Lys Ser Leu Glu Asn Leu Asn Arg Leu Gln Val Met Leu Leu
 1 5 10 15

His Leu Thr Ala Ala Phe Leu Gln Arg Ala Gln His Xaa Phe Asp Tyr
 20 25 30

Lys Asp Glu Ser Gly Phe Pro Lys Pro Pro Ser Tyr Asn Val Ala Thr
 35 40 45

Thr Leu Pro Ser Tyr Asp Glu Ala Glu Arg Thr Lys Ala Glu Ala Thr
 50 55 60

Ile Pro Leu Val Pro Gly Arg Asp Glu Asp Phe Val Gly Arg Asp Asp
 65 70 75 80

Phe Asp Asp Ala Asp Gln Leu Arg Ile Gly Asn Asp Gly Ile Phe Met
 85 90 95

Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe Leu
 100 105 110

Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile Ser
 115 120 125

Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe Ser
 130 135 140

Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp Val
 145 150 155 160

Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn Tyr
 165 170 175

Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg Thr

150

180

185

190

Arg-Val-Leu-Phe-Ile-Tyr
195

<210> 221
<211> 70
<212> PRT
<213> Homo sapiens

<400> 221
Met Leu Leu His Leu Thr Ala Ala Phe Leu Gln Arg Ala Gln Phe Ser
1 5 10 15

Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp-Trp Val
20 25 30

Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn Tyr
35 40 45

Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg Thr
50 55 60

Arg Val Leu Phe Ile Tyr
65 70

<210> 222
<211> 82
<212> PRT
<213> Homo sapiens

<400> 222
Met Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe
1 5 10 15

Leu Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile
20 25 30

Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe
35 40 45

Ser Thr Tyr Phe Pro Ala Phe Met Asn Ser Leu Ser Arg Ser Lys Arg
50 55 60

Thr Pro Ala Gly Ser Glu Ser Arg Cys Arg Thr Gln Arg Asn Asn His
65 70 75 80

Leu Leu

<210> 223
<211> 45
<212> PRT
<213> Homo sapiens

151

<220>

<221> SITE

<222> (28)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 223

Met Lys Lys Ser Leu Glu Asn Leu Asn Arg Leu Gln Val Met Leu Leu
 1 5 10 15

His Leu Thr Ala Ala Phe Leu Gln Arg Ala His Xaa Ile Leu Thr Thr
 20 25 30

Arg Met Ser Leu Gly Phe Gln Ser Pro His Leu Thr Met
 35 40 45

<210> 224

<211> 33

<212> PRT

<213> Homo sapiens

<400> 224

Met Thr Val Met Asp Pro Lys Gln Met Asn Val Ala Ala Ala Val Trp
 1 5 10 15

Ala Val Val Ser Tyr Val Val Ala Asp Met Glu Glu Met Leu Pro Arg
 20 25 30

Ser

<210> 225

<211> 189

<212> PRT

<213> Homo sapiens

<400> 225

Pro Arg Val Arg Ser Arg Glu Pro Val Ala Gly Ala Pro Gly Cys Gly
 1 5 10 15

Thr Ala Gly Pro Pro Ala Met Ala Thr Leu Trp Gly Gly Leu Leu Arg
 20 25 30

Leu Gly Ser Leu Leu Ser Leu Ser Cys Leu Ala Leu Ser Val Leu Leu
 35 40 45

Leu Ala His Cys Gln Thr Pro Pro Ser Asp Cys Leu His Val Val Glu
 50 55 60

Pro Met Pro Val Arg Gly Pro Asp Val Glu Ala Tyr Cys Leu Arg Cys
 65 70 75 80

Glu Cys Lys Tyr Glu Glu Arg Ser Ser Val Thr Ile Lys Val Thr Ile
 85 90 95

Ile Ile Tyr Leu Ser Ile Leu Gly Leu Leu Leu Leu Tyr Met Val Tyr
 100 105 110

152

Leu Thr Leu Val Glu Pro Ile Leu Lys Arg Arg Leu Phe Gly His Ala
 115 120 125

Gln Leu Ile Gln Ser Asp Asp Asp Ile Gly Asp His Gln Pro Phe Ala
 130 135 140

Asn Ala His Asp Val Leu Ala Arg Ser Arg Ser Arg Ala Asn Val Leu
 145 150 155 160

Asn Lys Val Glu Tyr Ala Gln Gln Arg Trp Lys Leu Gln Val Gln Glu
 165 170 175

Gln Arg Lys Ser Val Phe Asp Arg His Val Val Leu Ser
 180 185

<210> 226

<211> 231

<212> PRT

<213> Homo sapiens

<400> 226

Met Ala Thr Leu Trp Gly Gly Leu Leu Arg Leu Gly Ser Leu Leu Ser
 1 5 10 15

Leu Ser Cys Leu Ala Leu Ser Val Leu Leu Leu Ala His Cys Gln Thr
 20 25 30

Pro Pro Arg Ile Ser Arg Met Ser Asp Val Asn Val Ser Ala Leu Pro
 35 40 45

Ile Lys Lys Asn Ser Gly His Ile Tyr Asn Lys Asn Ile Ser Gln Lys
 50 55 60

Asp Cys Asp Cys Leu His Val Val Glu Pro Met Pro Val Arg Gly Pro
 65 70 75 80

Asp Val Glu Ala Tyr Cys Leu Arg Cys Glu Cys Lys Tyr Glu Glu Arg
 85 90 95

Ser Ser Val Thr Ile Lys Val Thr Ile Ile Ile Tyr Leu Ser Ile Leu
 100 105 110

Gly Leu Leu Leu Leu Tyr Met Val Tyr Leu Thr Leu Val Glu Pro Ile
 115 120 125

Leu Lys Arg Arg Leu Phe Gly His Ala Gln Leu Ile Gln Ser Asp Asp
 130 135 140

Asp Ile Gly Asp His Gln Pro Phe Ala Asn Ala His Asp Val Leu Ala
 145 150 155 160

Arg Ser Arg Ser Arg Ala Asn Val Leu Asn Lys Val Glu Tyr Gly Thr
 165 170 175

Ala Ala Leu Glu Ala Ser Ser Pro Arg Ala Ala Lys Ser Leu Ser Leu
 180 185 190

153

Thr Gly Met Leu Ser Ser Ala Asn Trp Gly Ile Glu Phe Lys Val Thr
 195 200 205

Arg Lys Lys Gln Ala Asp Asn Trp Lys Gly Thr Asp Trp Val Leu Leu
 210 215 220

Gly Phe Ile Leu Ile Pro Cys
 225 230

<210> 227

<211> 456

<212> PRT

<213> Homo-sapiens

<400> 227

Met Ala Ala Ala Gly Arg Leu Pro Ser Ser Trp Ala Leu Phe Ser Pro
 1 5 10 15

Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
 20 25 30

Ala Leu His Asn Val Thr Ala Glu Leu Phe Gly Ala Glu Ala Trp Gly
 35 40 45

Thr Leu Ala Ala Phe Gly Asp Leu Asn Ser Asp Lys Gln Thr Asp Leu
 50 55 60

Phe Val Leu Arg Glu Arg Asn Asp Leu Ile Val Phe Leu Ala Asp Gln
 65 70 75 80

Asn Ala Pro Tyr Phe Lys Pro Lys Val Lys Val Ser Phe Lys Asn His
 85 90 95

Ser Ala Leu Ile Thr Ser Val Val Pro Gly Asp Tyr Asp Gly Asp Ser
 100 105 110

Gln Met Asp Val Leu Leu Thr Tyr Leu Pro Lys Asn Tyr Ala Lys Ser
 115 120 125

Glu Leu Gly Ala Val Ile Phe Trp Gly Gln Asn Gln Thr Leu Asp Pro
 130 135 140

Asn Asn Met Thr Ile Leu Asn Arg Thr Phe Gln Asp Glu Pro Leu Ile
 145 150 155 160

Met Asp Phe Asn Gly Asp Leu Ile Pro Asp Ile Phe Gly Ile Thr Asn
 165 170 175

Glu Ser Asn Gln Pro Gln Ile Leu Leu Gly Gly Asn Leu Ser Trp His
 180 185 190

Pro Ala Leu Thr Thr Thr Ser Lys Met Arg Ile Pro His Ser His Ala
 195 200 205

Phe Ile Asp Leu Thr Glu Asp Phe Thr Ala Asp Leu Phe Leu Thr Thr
 210 215 220

154

Leu Asn Ala Thr Thr Ser Thr Phe Gln Phe Glu Ile Trp Glu Asn Leu
 225 230 235 240

Asp Gly Asn Phe Ser Val Ser Thr Ile Leu Glu Lys Pro Gln Asn Met
 245 250 255

Met Val Val Gly Gln Ser Ala Phe Ala Asp Phe Asp Gly Asp Gly His
 260 265 270

Met Asp His Leu Leu Pro Gly Cys Glu Asp Lys Asn Cys Gln Lys Ser
 275 280 285

Thr Ile Tyr Leu Val Arg Ser Gly Met Lys Gln Trp Val Pro Val Leu
 290 295 300

Gln Asp Phe Ser Asn Lys Gly Thr Leu Trp Gly Phe Val Pro Phe Val
 305 310 315 320

Asp Glu Gln Gln Pro Thr Glu Ile Pro Ile Pro Ile Thr Leu His Ile
 325 330 335

Gly Asp Tyr Asn Met Asp Gly Tyr Pro Asp Ala Leu Val Ile Leu Lys
 340 345 350

Asn Thr Ser Gly Ser Asn Gln Gln Ala Phe Leu Leu Glu Asn Val Pro
 355 360 365

Cys Asn Asn Ala Ser Cys Glu Glu Ala Arg Arg Met Phe Lys Val Tyr
 370 375 380

Trp Glu Leu Thr Asp Leu Asn Gln Ile Lys Asp Ala Met Val Ala Thr
 385 390 395 400

Phe Phe Asp Ile Tyr Glu Asp Gly Ile Leu Asp Ile Val Val Leu Ser
 405 410 415

Lys Gly Tyr Thr Lys Asn Asp Phe Ala Ile His Thr Leu Lys Asn Asn
 420 425 430

Phe Glu Ala Asp Ala Tyr Phe Val Lys Val Ile Val Leu Ser Gly Leu
 435 440 445

Cys Ser Asn Asp Cys Pro Arg Arg
 450 455

<210> 228

<211> 282

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (144)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

155

<221> SITE

<222> (168)

<223> Xaa_equals any of the naturally occurring L-amino acids

<400> 228

Met Thr Lys Arg Glu Asp Gly Gly Tyr Thr Phe Thr Ala Thr Pro Glu
 1 5 10 15

Asp Phe Pro Lys Lys His Lys Ala Pro Val Ile Asp Ile Gly Ile Ala
 20 25 30

Asn Thr Gly Lys Phe Ile Met Thr Ala Ser Ser Asp Thr Thr Val Leu
 35 40 45

Ile Trp Ser Leu Lys Gly Gln Val Leu Ser Thr Ile Asn Thr Asn Gln
 50 55 60

Met Asn Asn Thr His Ala Ala Val Ser Pro Cys Gly Arg Phe Val Ala
 65 70 75 80

Ser Cys Gly Phe Thr Pro Asp Val Lys Val Trp Glu Val Cys Phe Gly
 85 90 95

Lys Lys Gly Glu Phe Gln Glu Val Val Arg Ala Phe Glu Leu Lys Gly
 100 105 110

His Ser Ala Ala Val His Ser Phe Ala Phe Ser Asn Asp Ser Arg Arg
 115 120 125

Met Ala Ser Val Ser Lys Asp Gly Thr Trp Lys Leu Trp Asp Thr Xaa
 130 135 140

Val Glu Tyr Lys Lys Lys Gln Asp Pro Tyr Leu Leu Lys Thr Gly Arg
 145 150 155 160

Phe Glu Glu Ala Ala Gly Ala Xaa Pro Cys Arg Leu Ala Leu Ser Pro
 165 170 175

Asn Ala Gln Val Leu Ala Leu Ala Ser Gly Ser Ser Ile His Leu Tyr
 180 185 190

Asn Thr Arg Arg Gly Glu Lys Glu Glu Cys Phe Glu Arg Val His Gly
 195 200 205

Glu Cys Ile Ala Asn Leu Ser Phe Asp Ile Thr Gly Arg Phe Leu Ala
 210 215 220

Ser Cys Gly Asp Arg Ala Val Arg Leu Phe His Asn Thr Pro Gly His
 225 230 235 240

Arg Ala Met Val Glu Glu Met Gln Gly His Leu Lys Arg Ala Ser Asn
 245 250 255

Glu Ser Thr Arg Gln Arg Leu Gln Gln Gln Leu Thr Gln Ala Gln Glu
 260 265 270

Thr Leu Lys Ser Leu Gly Ala Leu Lys Lys
 275 280

<210> 229
 <211> 456
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (17)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (37)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (318)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (342)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 229
 Val Ile Arg His Glu Gly Ser Thr Asn Met Glu Leu Ser Gln Met Ser
 1 5 10 15
 Xaa Leu Met Gly Leu Ser Val Leu Leu Gly Leu Leu Ala Leu Met Ala
 20 25 30
 Thr Ala Ala Val Xaa Arg Gly Trp Leu Arg Ala Gly Glu Arg Ser
 35 40 45
 Gly Arg Pro Ala Cys Gln Lys Ala Asn Gly Phe Pro Pro Asp Lys Ser
 50 55 60
 Ser Gly Ser Lys Lys Gln Lys Gln Tyr Gln Arg Ile Arg Lys Glu Lys
 65 70 75 80
 Pro Gln Gln His Asn Phe Thr His Arg Leu Leu Ala Ala Ala Leu Lys
 85 90 95
 Ser His Ser Gly Asn Ile Ser Cys Met Asp Phe Ser Ser Asn Gly Lys
 100 105 110
 Tyr Leu Ala Thr Cys Ala Asp Asp Arg Thr Ile Arg Ile Trp Ser Thr
 115 120 125
 Lys Asp Phe Leu Gln Arg Glu His Arg Ser Met Arg Ala Asn Val Glu
 130 135 140
 Leu Asp His Ala Thr Leu Val Arg Phe Ser Pro Asp Cys Arg Ala Phe
 145 150 155 160

157

Ile Val Trp Leu Ala Asn Gly Asp Thr Leu Arg Val Phe Lys Met Thr
 165 170 175

Lys Arg Glu Asp Gly Gly Tyr Thr Phe Thr Ala Thr Pro Glu Asp Phe
 180 185 190

Pro Lys Lys His Lys Ala Pro Val Ile Asp Ile Gly Ile Ala Asn Thr
 195 200 205

Gly Lys Phe Ile Met Thr Ala Ser Ser Asp Thr Thr Val Leu Ile Trp
 210 215 220

Ser Leu Lys Gly Gln Val Leu Ser Thr Ile Asn Thr Asn Gln Met Asn
 225 230 235 240

Asn Thr His Ala Ala Val Ser Pro Cys Gly Arg Phe Val Ala Ser Cys
 245 250 255

Gly Phe Thr Pro Asp Val Lys Val Trp Glu Val Cys Phe Gly Lys Lys
 260 265 270

Gly Glu Phe Gln Glu Val Val Arg Ala Phe Glu Leu Lys Gly His Ser
 275 280 285

Ala Ala Val His Ser Phe Ala Phe Ser Asn Asp Ser Arg Arg Met Ala
 290 295 300

Ser Val Ser Lys Asp Gly Thr Trp Lys Leu Trp Asp Thr Xaa Val Glu
 305 310 315 320

Tyr Lys Lys Lys Gln Asp Pro Tyr Leu Leu Lys Thr Gly Arg Phe Glu
 325 330 335

Glu Ala Ala Gly Ala Xaa Pro Cys Arg Leu Ala Leu Ser Pro Asn Ala
 340 345 350

Gln Val Leu Ala Leu Ala Ser Gly Ser Ser Ile His Leu Tyr Asn Thr
 355 360 365

Arg Arg Gly Glu Lys Glu Glu Cys Phe Glu Arg Val His Gly Glu Cys
 370 375 380

Ile Ala Asn Leu Ser Phe Asp Ile Thr Gly Arg Phe Leu Ala Ser Cys
 385 390 395 400

Gly Asp Arg Ala Val Arg Leu Phe His Asn Thr Pro Gly His Arg Ala
 405 410 415

Met Val Glu Glu Met Gln Gly His Leu Lys Arg Ala Ser Asn Glu Ser
 420 425 430

Thr Arg Gln Arg Leu Gln Gln Gln Leu Thr Gln Ala Gln Glu Thr Leu
 435 440 445

Lys Ser Leu Gly Ala Leu Lys Lys
 450 455

158

<210> 230

<211> 363

<212> PRT

<213> Homo sapiens

<400> 230

Met Ser Val Met Val Val Arg Lys Lys Val Thr Arg Lys Trp Glu Lys
 1 5 10 15

Leu Pro Gly Arg Asn Thr Phe Cys Cys Asp Gly Arg Val Met Met Ala
 20 25 30

Arg Gln Lys Gly Ile Phe Tyr Leu Thr Leu Phe Leu Ile Leu Gly Thr
 35 40 45

Cys Thr Leu Phe Phe Ala Phe Glu Cys Arg Tyr Leu Ala Val Gln Leu
 50 55 60

Ser Pro Ala Ile Pro Val Phe Ala Ala Met Leu Phe Leu Phe Ser Met
 65 70 75 80

Ala Thr Leu Leu Arg Thr Ser Phe Ser Asp Pro Gly Val Ile Pro Arg
 85 90 95

Ala Leu Pro Asp Glu Ala Ala Phe Ile Glu Met Glu Ile Glu Ala Thr
 100 105 110

Asn Gly Ala Val Pro Gln Gly Gln Arg Pro Pro Pro Arg Ile Lys Asn
 115 120 125

Phe Gln Ile Asn Asn Gln Ile Val Lys Leu Lys Tyr Cys Tyr Thr Cys
 130 135 140

Lys Ile Phe Arg Pro Pro Arg Ala Ser His Cys Ser Ile Cys Asp Asn
 145 150 155 160

Cys Val Glu Arg Phe Asp His His Cys Pro Trp Val Gly Asn Cys Val
 165 170 175

Gly Lys Arg Asn Tyr Arg Tyr Phe Tyr Leu Phe Ile Leu Ser Leu Ser
 180 185 190

Leu Leu Thr Ile Tyr Val Phe Ala Phe Asn Ile Val Tyr Val Ala Leu
 195 200 205

Lys Ser Leu Lys Ile Gly Phe Leu Glu Thr Leu Lys Glu Thr Pro Gly
 210 215 220

Thr Val Leu Glu Val Leu Ile Cys Phe Phe Thr Leu Trp Ser Val Val
 225 230 235 240

Gly Leu Thr Gly Phe His Thr Phe Leu Val Ala Leu Asn Gln Thr Thr
 245 250 255

Asn Glu Asp Ile Lys Gly Ser Trp Thr Gly Lys Asn Arg Val Gln Asn
 260 265 270

Pro Tyr Ser His Gly Asn Ile Val Lys Asn Cys Cys Glu Val Leu Cys

159

275

280

285

Gly-Pro-Leu-Pro-Pro-Ser-Val-Leu-Asp-Arg-Arg-Gly-Ile-Leu-Pro-Leu
 290 295 300

Glu-Glu-Ser-Gly-Ser-Arg-Pro-Pro-Ser-Thr-Gln-Glu-Thr-Ser-Ser-Ser
 305 310 315 320

Leu-Leu-Pro-Gln-Ser-Pro-Ala-Pro-Thr-Glu-Leu-Asn-Ser-Asn-Glu-Met
 325 330 335

Pro-Glu-Asp-Ser-Ser-Thr-Pro-Glu-Glu-Met-Pro-Pro-Pro-Glu-Pro-Pro
 340 345 350

Glu-Pro-Pro-Gln-Glu-Ala-Ala-Glu-Ala-Glu-Lys
 355 360

<210> 231

<211> 184

<212> PRT

<213> Homo sapiens

<400> 231

Met-Leu-Phe-Leu-Phe-Ser-Met-Ala-Thr-Leu-Leu-Arg-Thr-Ser-Phe-Ser
 1 5 10 15

Asp-Pro-Gly-Val-Ile-Pro-Arg-Ala-Leu-Pro-Asp-Glu-Ala-Ala-Phe-Ile
 20 25 30

Glu-Met-Glu-Ile-Glu-Ala-Thr-Asn-Gly-Ala-Val-Pro-Gln-Gly-Gln-Arg
 35 40 45

Pro-Pro-Pro-Arg-Ile-Lys-Asn-Phe-Gln-Ile-Asn-Asn-Gln-Ile-Val-Lys
 50 55 60

Leu-Lys-Tyr-Cys-Tyr-Thr-Cys-Lys-Ile-Phe-Arg-Pro-Pro-Arg-Ala-Ser
 65 70 75 80

His-Cys-Ser-Ile-Cys-Asp-Asn-Cys-Val-Glu-Arg-Phe-Asp-His-His-Cys
 85 90 95

Pro-Trp-Val-Gly-Asn-Cys-Val-Gly-Lys-Arg-Asn-Tyr-Arg-Tyr-Phe-Tyr
 100 105 110

Leu-Phe-Ile-Leu-Ser-Leu-Ser-Leu-Leu-Thr-Ile-Tyr-Val-Phe-Ala-Phe
 115 120 125

Asn-Ile-Val-Tyr-Val-Ala-Leu-Lys-Ser-Leu-Lys-Ile-Gly-Phe-Leu-Glu
 130 135 140

Thr-Leu-Lys-Gly-Asn-Ser-Trp-Asn-Cys-Ser-Arg-Ser-Pro-His-Leu-Leu
 145 150 155 160

Leu-Tyr-Thr-Leu-Val-Arg-Arg-Gly-Thr-Asp-Trp-Ile-Ser-Tyr-Phe-Pro
 165 170 175

Arg-Gly-Ser-Gln-Pro-Asp-Asn-Gln

160

180

<210> 232

<211> 52

<212> PRT

<213> Homo sapiens

<400> 232

Leu His Glu Cys Leu Pro Gly Ser Ile Ser Tyr Leu His Pro Arg Thr
 1 5 10 15

Pro Trp Leu Cys Leu Pro Pro Gln His Leu Ser Phe Ser Thr Phe Ser
 20 25 30

Pro Pro Trp Gln Pro Ala Met Ser Pro Val Pro Gly Thr Gly Gly Pro
 35 40 45

Pro Cys Gly Leu
 50

<210> 233

<211> 177

<212> PRT

<213> Homo sapiens

<400> 233

Met Leu Pro Leu Leu Ile Ile Cys Leu Leu Pro Ala Ile Glu Gly Lys
 1 5 10 15

Asn Cys Leu Arg Cys Trp Pro Glu Leu Ser Ala Leu Ile Asp Tyr Asp
 20 25 30

Leu Gln Ile Leu Trp Val Thr Pro Gly Pro Pro Thr Glu Leu Ser Gln
 35 40 45

Ser Ile His Ser Leu Phe Leu Glu Asp Asn Asn Phe Leu Lys Pro Trp
 50 55 60

Tyr Leu Asp Arg Asp His Leu Glu Glu Glu Thr Ala Lys Phe Phe Thr
 65 70 75 80

Gln Val His Gln Ala Ile Lys Thr Leu Arg Asp Asp Lys Thr Val Leu
 85 90 95

Leu Glu Glu Ile Tyr Thr His Lys Asn Leu Phe Thr Glu Arg Leu Asn
 100 105 110

Lys Ile Ser Asp Gly Leu Lys Glu Lys Gly Ala Pro Pro Leu His Glu
 115 120 125

Cys Leu Pro Gly Ser Ile Ser Tyr Leu His Pro Arg Thr Pro Trp Leu
 130 135 140

Cys Leu Pro Pro Gln His Leu Ser Phe Ser Thr Phe Ser Pro Pro Trp
 145 150 155 160

161

Gln Pro Ala Met Ser Pro Val Pro Gly Thr Gly Gly Pro Pro Cys Gly
 165 170 175

Leu

<210> 234

<211> 95

<212> PRT

<213> Homo sapiens

<400> 234

Pro Pro Val Pro Pro Trp Ile Ser Leu Pro Leu Thr Gly Ser Pro Pro
 1 5 10 15

Arg Pro Gly Phe Val Pro Val Ser Pro Phe Cys Phe Ser Pro Met Thr
 20 25 30

Asn Gly His Gln Val Leu Leu Leu Leu Leu Thr Ser Ala Val Ala
 35 40 45

Ala Gly Pro Trp Pro Gln Val His Ala Gly Gln Trp Gly Trp Met Cys
 50 55 60

Leu Pro Pro Gly Leu Pro Ser Val Gln Ala Arg Ser Gly Leu Gly Gly
 65 70 75 80

Leu Pro Gly Gly Pro Gln Trp Val Pro Gly Gly Ala Arg Gly Tyr
 85 90 95

<210> 235

<211> 404

<212> PRT

<213> Homo sapiens

<400> 235

Ile Gln Gln Trp Gly Asp Ser Val Leu Gly Arg Arg Cys Arg Asp Leu
 1 5 10 15

Leu Leu Gln Leu Tyr Leu Gln Arg Pro Glu Leu Arg Val Pro Val Pro
 20 25 30

Glu Val Leu Leu His Ser Glu Gly Ala Ala Ser Ser Ser Val Cys Lys
 35 40 45

Leu Asp Gly Leu Ile His Arg Phe Ile Thr Leu Leu Ala Asp Thr Ser
 50 55 60

Asp Ser Arg Ala Leu Glu Asn Arg Gly Ala Asp Ala Ser Met Ala Cys
 65 70 75 80

Arg Lys Leu Ala Val Ala His Pro Leu Leu Leu Leu Arg His Leu Pro
 85 90 95

Met Ile Ala Ala Leu Leu His Gly Arg Thr His Leu Asn Phe Gln Glu
 100 105 110

162

Phe Arg Gln Gln Asn His Leu Ser Cys Phe Leu His Val Leu Gly Leu
 115 120 125

Leu Glu Leu Leu Gln Pro His Val Phe Arg Ser Glu His Gln Gly Ala
 130 135 140

Leu Trp Asp Cys Leu Leu Ser Phe Ile Arg Leu Leu Leu Asn Tyr Arg
 145 150 155 160

Lys Ser Ser Arg His Leu Ala Ala Phe Ile Asn Lys Phe Val Gln Phe
 165 170 175

Ile His Lys Tyr Ile Thr Tyr Asn Ala Pro Ala Ala Ile Ser Phe Leu
 180 185 190

Gln Lys His Ala Asp Pro Leu His Asp Leu Ser Phe Asp Asn Ser Asp
 195 200 205

Leu Val Met Leu Lys Ser Leu Leu Ala Gly Leu Ser Leu Pro Ser Arg
 210 215 220

Asp Asp Arg Thr Asp Arg Gly Leu Asp Glu Glu Gly Glu Glu Ser
 225 230 235 240

Ser Ala Gly Ser Leu Pro Leu Val Ser Val Ser Leu Phe Thr Pro Leu
 245 250 255

Thr Ala Ala Glu Met Ala Pro Tyr Met Lys Arg Leu Ser Arg Gly Gln
 260 265 270

Thr Val Glu Asp Leu Leu Glu Val Leu Ser Asp Ile Asp Glu Met Ser
 275 280 285

Arg Arg Arg Pro Glu Ile Leu Ser Phe Phe Ser Thr Asn Leu Gln Arg
 290 295 300

Leu Met Ser Ser Ala Glu Glu Cys Cys Arg Asn Leu Ala Phe Ser Leu
 305 310 315 320

Ala Leu Arg Ser Met Gln Asn Ser Pro Ser Ile Ala Ala Ala Phe Leu
 325 330 335

Pro Thr Phe Met Tyr Cys Leu Gly Ser Gln Asp Phe Glu Val Val Gln
 340 345 350

Thr Ala Leu Arg Asn Leu Pro Glu Tyr Ala Leu Leu Cys Gln Glu His
 355 360 365

Ala Ala Val Leu Leu His Arg Ala Phe Leu Val Gly Met Tyr Gly Gln
 370 375 380

Met Asp Pro Ser Ala Gln Ile Ser Glu Ala Leu Arg Ile Leu His Met
 385 390 395 400

Glu Ala Val Met

163

<210> 236

<211> 361

<212> PRT

<213> Homo sapiens

<400> 236

Met Leu Leu Lys His Leu Gln Arg Met Val Ser Val Pro Gln Val Lys

1 5 10 15

Ala Ser Ala Leu Lys Val Val Thr Leu Thr Ala Asn Asp Lys Thr Ser

20 25 30

Val Ser Phe Ser Ser Leu Pro Gly Gln Gly Val Ile Tyr Asn Val Ile

35 40 45

Val Trp Asp Pro Phe Leu Asn Thr Ser Ala Ala Tyr Ile Pro Ala His

50 55 60

Thr Tyr Ala Cys Ser Phe Glu Ala Gly Glu Gly Ser Cys Ala Ser Leu

65 70 75 80

Gly Arg Val Ser Ser Lys Val Phe Phe Thr Leu Phe Ala Leu Leu Gly

85 90 95

Phe Phe Ile Cys Phe Phe Gly His Arg Phe Trp Lys Thr Glu Leu Phe

100 105 110

Phe Ile Gly Phe Ile Ile Met Gly Phe Phe Phe Tyr Ile Leu Ile Thr

115 120 125

Arg Leu Thr Pro Ile Lys Tyr Asp Val Asn Leu Ile Leu Thr Ala Val

130 135 140

Thr Gly Ser Val Gly Gly Met Phe Leu Val Ala Val Trp Trp Arg Phe

145 150 155 160

Gly Ile Leu Ser Ile Cys Met Leu Cys Val Gly Leu Val Leu Gly Phe

165 170 175

Leu Ile Ser Ser Val Thr Phe Phe Thr Pro Leu Gly Asn Leu Lys Ile

180 185 190

Phe His Asp Asp Gly Val Phe Trp Val Thr Phe Ser Cys Ile Ala Ile

195 200 205

Leu Ile Pro Val Val Phe Met Gly Cys Leu Arg Ile Leu Asn Ile Leu

210 215 220

Thr Cys Gly Val Ile Gly Ser Tyr Ser Val Val Leu Ala Ile Asp Ser

225 230 235 240

Tyr Trp Ser Thr Ser Leu Ser Tyr Ile Thr Leu Asn Val Leu Lys Arg

245 250 255

Ala Leu Asn Lys Asp Phe His Arg Ala Phe Thr Asn Val Pro Phe Gln

260 265 270

164

Thr Asn Asp Phe Ile Ile Leu Ala Val Trp Gly Met Leu Ala Val Ser
 275 280 285

Gly Ile Thr Leu Gln Ile Arg Arg Glu Arg Gly Arg Pro Phe Phe Pro
 290 295 300

Pro His Pro Tyr Lys Leu Trp Lys Gln Glu Arg Glu Arg Arg Val Thr
 305 310 315 320

Asn Ile Leu Asp Pro Ser Tyr His Ile Pro Pro Leu Arg Glu Arg Leu
 325 330 335

Tyr Gly Arg Leu Thr Gln Ile Lys Gly Leu Phe Gln Lys Glu Gln Pro
 340 345 350

Ala Gly Glu Arg Thr Pro Leu Leu Leu
 355 360

<210> 237

<211> 116

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (37)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (40)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 237

Trp Ala Arg Leu Arg Gly Pro Gly Ala His Ala Arg Thr Ser Pro Gln
 1 5 10 15

Pro Trp Arg Gly Pro Ser Pro Ala Gln Ala Ala Met Gly Phe Leu Gln
 20 25 30

Leu Leu Val Val Xaa Val Leu Xaa Ser Glu His Arg Val Ala Gly Ala
 35 40 45

Ala Glu Val Phe Gly Asn Ser Ser Glu Gly Leu Ile Glu Phe Ser Val
 50 55 60

Gly Lys Phe Arg Tyr Phe Glu Leu Asn Arg Pro Phe Pro Glu Glu Ala
 65 70 75 80

Ile Leu His Asp Ile Ser Ser Asn Val Thr Phe Leu Ile Phe Gln Ile
 85 90 95

His Ser Gln Tyr Gln Asn Thr Thr Val Ser Phe Ser Pro Arg Arg Arg
 100 105 110

Ser Pro Thr Met
 115

165

<210> 238

<211> 166

<212> PRT

<213> Homo sapiens

<400> 238

Pro Arg Val Arg Pro Ala Ser Pro Pro Val Arg Ser Pro Ala Arg Trp
 1 5 10 15

Gly Ser Met Ala Gly Ser Pro Leu Leu Trp Gly Pro Arg Ala Gly Gly
 20 25 30

Val Gly Leu Leu Val Leu Leu Leu Gly Leu Phe Arg Pro Pro Pro
 35 40 45

Ala Leu Cys Ala Arg Pro Val Lys Glu Pro Arg Gly Leu Ser Ala Ala
 50 55 60

Ser Pro Pro Leu Ala Arg Leu Ala Leu Leu Ala Ala Ser Gly Gly Gln
 65 70 75 80

Cys Pro Glu Val Arg Arg Arg Gly Arg Cys Arg Pro Gly Ala Gly Ala
 85 90 95

Gly Ala Ser Ala Gly Ala Glu Arg Gln Glu Arg Ala Arg Ala Glu Ala
 100 105 110

Gln Arg Leu Arg Ile Ser Arg Arg Ala Ser Trp Arg Ser Cys Cys Ala
 115 120 125

Ser Gly Ala Pro Pro Ala Thr Leu Ile Arg Leu Trp Ala Trp Thr Thr
 130 135 140

Thr Pro Thr Arg Leu Gln Arg Ser Ser Leu Ala Leu Cys Ser Ala Pro
 145 150 155 160

Ala Leu Thr Leu Pro Pro
 165

<210> 239

<211> 414

<212> PRT

<213> Homo sapiens

<400> 239

Pro Arg Val Arg Leu Ala Thr Pro Asn Ile Trp Asp Leu Ser Met Leu
 1 5 10 15

Phe Ala Phe Ile Ser Leu Leu Val Met Leu Pro Thr Trp Trp Ile Val
 20 25 30

Ser Ser Trp Leu Val Trp Gly Val Ile Leu Phe Val Tyr Leu Val Ile
 35 40 45

Arg Ala Leu Arg Leu Trp Arg Thr Ala Lys Leu Gln Val Thr Leu Lys

166

50

55

60

~~Lys-Tyr-Ser-Val-His-Leu-Glu-Asp-Met-Ala-Thr-Asn-Ser-Arg-Ala-Phe~~
~~65 70 75 80~~

Thr Asn Leu Val Arg Lys Ala Leu Arg Leu Ile Gln Glu Thr Glu Val
 85 90 95

Ile Ser Arg Gly Phe Thr Leu Val Ser Ala Ala Cys Pro Phe Asn Lys
 100 105 110

Ala Gly Gln His Pro Ser Gln His Leu Ile Gly Leu Arg Lys Ala Val
 115 120 125

Tyr Arg Thr Leu Arg Ala Asn Phe Gln Ala Ala Arg Leu Ala Thr Leu
 130 135 140

Tyr Met Leu Lys Asn Tyr Pro Leu Asn Ser Glu Ser Asp Asn Val Thr
 145 150 155 160

Asn Tyr Ile Cys Val Val Pro Phe Lys Glu Leu Gly Leu Gly Leu Ser
 165 170 175

Glu Glu Gln Ile Ser Glu Glu Glu Ala His Asn Phe Thr Asp Gly Phe
 180 185 190

Ser Leu Pro Ala Leu Lys Val Leu Phe Gln Leu Trp Val Ala Gln Ser
 195 200 205

Ser Glu Phe Phe Arg Arg Leu Ala Leu Leu Leu Ser Thr Ala Asn Ser
 210 215 220

Pro Pro Gly Pro Leu Leu Thr Pro Ala Leu Leu Pro His Arg Ile Leu
 225 230 235 240

Ser Asp Val Thr Gln Gly Leu Pro His Ala His Ser Ala Cys Leu Glu
 245 250 255

Glu Leu Lys Arg Ser Tyr Glu Phe Tyr Arg Tyr Phe Glu Thr Gln His
 260 265 270

Gln Ser Val Pro Gln Cys Leu Ser Lys Thr Gln Gln Lys Ser Arg Glu
 275 280 285

Leu Asn Asn Val His Thr Ala Val Arg Ser Leu Gln Leu His Leu Lys
 290 295 300

Ala Leu Leu Asn Glu Val Ile Ile Leu Glu Asp Glu Leu Glu Lys Leu
 305 310 315 320

Val Cys Thr Lys Glu Thr Gln Glu Leu Val Ser Glu Ala Tyr Pro Ile
 325 330 335

Leu Glu Gln Lys Leu Lys Leu Ile Gln Pro His Val Gln Ala Ser Asn
 340 345 350

Asn Cys Trp Glu Glu Ala Ile Ser Gln Val Asp Lys Leu Leu Arg Arg
 355 360 365

167

Asn Thr Asp Lys Lys Gly Lys Pro Glu Ile Ala Cys Glu Asn Pro His
 370 375 380

Cys Thr Val Ser Thr Phe Glu Ala Ala Tyr Ser Thr His Cys Arg Gln
 385 390 395 400

Arg Ser Asn Pro Arg Gly Ala Gly Ile Arg Ser Leu Cys Arg
 405 410

<210> 240

<211> 145

<212> PRT

<213> Homo sapiens

<400> 240

Ala Ala Pro His Pro Pro Leu Leu Arg Pro Leu Cys Leu Trp Cys Pro
 1 5 10 15

Leu Trp Pro Ala Trp Pro Leu Arg Gly Arg Pro Arg Ser Ala Trp Lys
 20 25 30

Arg Trp Pro Pro Leu Pro Val Gly Pro Ala Lys Leu Gly Cys Ser Met
 35 40 45

Thr Thr Arg Gln Pro Thr Ala Val Ser Trp Pro Cys Trp Leu Met Ser
 50 55 60

Ser Ser Leu Ser Thr Ala Cys Leu Ala Trp Thr Leu Thr Gly Ser Leu
 65 70 75 80

Ala Arg Glu Ala Thr Arg Arg Ala Arg Ser Leu Ser Pro Thr Trp Asn
 85 90 95

Cys Ser Ala Arg Gln Val Pro Pro Ser Pro Pro His Ser Gly Leu Gly
 100 105 110

Arg Arg Gly Trp Ala His Cys His Leu Thr Cys Leu Leu Val Thr Gln
 115 120 125

Leu Phe Arg Val Gly Arg Ile His Pro Ile Leu Ser Leu Pro Leu Val
 130 135 140

Thr
 145

<210> 241

<211> 72

<212> PRT

<213> Homo sapiens

<400> 241

Leu Gln Leu Ala Ser Gln Ser Ala Gly Ile Lys Gly Met Ser His Cys
 1 5 10 15

Ala Arg Pro Thr Phe Leu Thr Leu Leu Leu Ala Ser Cys Phe Trp Ala

168

20

25

30

Ala Ala Ile Pro Asn Arg Asn Val Ile Leu Ser Val Ser Phe Arg Pro
 35 40 45

Leu His Met Gln Phe Thr Leu Ser Ile Leu Val Phe Ile Leu Arg Ile
 50 55 60

Leu Ile Leu Leu Arg Ser Phe Leu
 65 70

<210> 242

<211> 140

<212> PRT

<213> Homo sapiens

<400> 242

Met Val Leu Val Leu Arg His Pro Leu Cys Ala Arg Glu Arg Ala Phe
 1 5 10 15

Arg Glu Pro Gly Arg Gly Leu Leu Thr Arg Thr Gly Gln His Asp Gly
 20 25 30

Ala Pro Ala Val Thr Ala Val Pro Gly Pro Leu Gly Ala Val Ala Ala
 35 40 45

Ala Glu Gly Arg Arg Ser Ala Trp Gly Ala Gly Gly Ser Ser Pro Pro
 50 55 60

Arg Lys Val Leu Trp Gly Asp Met Arg Gly Arg Arg Ala Gly Val Asp
 65 70 75 80

Val Leu Gly Pro Ala Leu Ser Ser Glu Ala Ala Gly Ala Glu Ala Arg
 85 90 95

Gly Trp Gly Met Pro Gly Met Gly Val Gly Val Gly Ala Ser Glu Thr
 100 105 110

Arg Gly Ala Leu Phe Leu Gly Arg Glu Gly Val His Gly Pro Cys Pro
 115 120 125

Met Asp Gly Leu Gly Pro Trp Pro Trp Gly Pro Trp
 130 135 140

<210> 243

<211> 353

<212> PRT

<213> Homo sapiens

<400> 243

Met Gly Pro Ala Val Lys Met Trp Thr Asn Ala Trp Lys Gly Leu Asp
 1 5 10 15

Asp Cys His Tyr Asn Gln Leu Cys Glu Asn Thr Pro Gly Gly His Arg
 20 25 30

169

Cys Ser Cys Pro Arg Gly Tyr Arg Met Gln Gly Pro Ser Leu Pro Cys
 35 40 45

~~Leu-Asp-Val-Asn-Glu-Cys-Leu-Gln-Leu-Pro-Lys-Ala-Cys-Ala-Tyr-Gln~~
 50 55 60

Cys His Asn Leu Gln Gly Ser Tyr Arg Cys Leu Cys Pro Pro Gly Gln
 65 70 75 80

Thr Leu Leu Arg Asp Gly Lys Ala Cys Thr Ser Leu Glu Arg Asn Gly
 85 90 95

Gln Asn Val Thr Thr Val Ser His Arg Gly Pro Leu Leu Pro Trp Leu
 100 105 110

~~Arg-Pro-Trp-Ala-Ser-Ile-Pro-Gly-Thr-Ser-Tyr-His-Ala-Trp-Val-Ser~~
 115 120 125

Leu Arg Pro Gly Pro Met Ala Leu Ser Ser Val Gly Arg Ala Trp Cys
 130 135 140

Pro Pro Gly Phe Ile Arg Gln Asn Gly Val Cys Thr Asp Leu Asp Glu
 145 150 155 160

Cys Arg Val Arg Asn Leu Cys Gln His Ala Cys Arg Asn Thr Glu Gly
 165 170 175

Ser Tyr Gln Cys Leu Cys Pro Ala Gly Tyr Arg Leu Leu Pro Ser Gly
 180 185 190

Lys Asn Cys Gln Asp Ile Asn Glu Cys Glu Glu Glu Ser Ile Glu Cys
 195 200 205

Gly Pro Gly Gln Met Cys Phe Asn Thr Arg Gly Ser Tyr Gln Cys Val
 210 215 220

Asp Thr Pro Cys Pro Ala Thr Tyr Arg Gln Gly Pro Ser Pro Gly Thr
 225 230 235 240

Cys Phe Arg Arg Cys Ser Gln Asp Cys Gly Thr Gly Gly Pro Ser Thr
 245 250 255

Leu Gln Tyr Arg Leu Leu Pro Leu Pro Leu Gly Val Arg Ala His His
 260 265 270

Asp Val Ala Arg Leu Thr Ala Phe Ser Glu Val Gly Val Pro Ala Asn
 275 280 285

Arg Thr Glu Leu Ser Met Leu Glu Pro Asp Pro Arg Ser Pro Phe Ala
 290 295 300

Leu Arg Pro Leu Arg Ala Gly Leu Gly Ala Val Tyr Thr Arg Arg Ala
 305 310 315 320

Leu Thr Arg Ala Gly Leu Tyr Arg Leu Thr Val Arg Ala Ala Ala Pro
 325 330 335

Arg His Gln Ser Val Phe Val Leu Leu Ile Ala Val Ser Pro Tyr Pro

170

340

345

350

Tyr

<210> 244

<211> 146

<212> PRT

<213> Homo sapiens

<400> 244

Met Arg Val Leu Val Val Thr Ile Ala Pro Ile Tyr Trp Ala Leu Ala
 1 5 10 15

-----Arg Glu Ser Gly Glu Ala Leu Asn Gly His Ser Leu Thr Gly Gly Lys-----
 20 25 30

Phe Arg Gln Ser His Thr Trp Ser Leu Leu Gln Gly Ala Ala His Asp
 35 40 45

Asp Pro Val Ala Arg Gly Leu Asp Pro Asp Gly Leu Leu Leu Asp
 50 55 60

Val Val Val Asn Gly Val Val Pro Gly Arg Ala Trp Leu Thr Gln Ile
 65 70 75 80

Phe Lys Cys Arg Thr Leu Lys Lys His Tyr Val Gln Thr Arg Ala Trp
 85 90 95

Pro Ala Val Arg Gly Leu His Thr Ala Leu Leu Pro Gly Arg Pro Pro
 100 105 110

Leu Val Pro Thr Leu Gln Pro Gln His Pro Val Gln Arg Gly Pro Gly
 115 120 125

Pro Pro Ala Pro Ala Gly Ala Ala Pro Ala Gly Leu Ser Tyr Gln Leu
 130 135 140

Gly Leu
 145

<210> 245

<211> 638

<212> PRT

<213> Homo sapiens

<400> 245

His Ala Ser Gly Ala Phe Leu Val Val Arg Gly Glu Pro Gln Gly Ser
 1 5 10 15

Trp Gly Ser Met Thr Gly Val Ile Asn Gly Arg Lys Phe Gly Val Ala
 20 25 30

Thr Leu Asn Thr Ser Val Met Gln Glu Ala His Ser Gly Val Ser Ser
 35 40 45

171

Ile His Ser Ser Ile Arg His Val Pro Ala Asn Val Gly Pro Leu Met
50 55 60

~~Arg Val Leu Val Val Thr Ile Ala Pro Ile Tyr Trp Ala Leu Ala Arg~~
65 70 75 80

Glu Ser Gly Glu Ala Leu Asn Gly His Ser Leu Thr Gly Gly Lys Phe
85 90 95

Arg Gln Glu Ser His Val Glu Phe Ala Thr Gly Glu Leu Leu Thr Met
100 105 110

Thr Gln Trp Pro Gly Val Trp Ile Pro Met Ala Ser Cys Ser Ser Thr
115 120 125

~~Trp Trp Ser Met Ala Leu Ser Pro Asp Ser Leu Ala Asp Ala Asp Leu~~
130 135 140

Gln Val Gln Asp Phe Glu Glu His Tyr Val Gln Thr Gly Pro Gly Gln
145 150 155 160

Leu Phe Val Gly Ser Thr Gln Arg Phe Phe Gln Gly Gly Leu Pro Ser
165 170 175

Phe Leu Arg Cys Asn His Ser Ile Gln Tyr Asn Ala Ala Arg Gly Pro
180 185 190

Gln Pro Gln Leu Val Gln His Leu Arg Ala Ser Ala Ile Ser Ser Ala
195 200 205

Phe Asp Pro Glu Ala Glu Ala Leu Arg Phe Gln Leu Ala Thr Ala Leu
210 215 220

Gln Ala Glu Glu Asn Glu Val Gly Cys Pro Glu Gly Phe Glu Leu Asp
225 230 235 240

Ser Gln Gly Ala Phe Cys Val Asp Val Asp Glu Cys Ala Trp Asp Ala
245 250 255

His Leu Cys Arg Glu Gly Gln Arg Cys Val Asn Leu Leu Gly Ser Tyr
260 265 270

Arg Cys Leu Pro Asp Cys Gly Pro Gly Phe Arg Val Ala Asp Gly Ala
275 280 285

Gly Cys Glu Asp Val Asp Glu Cys Leu Glu Gly Leu Asp Asp Cys His
290 295 300

Tyr Asn Gln Leu Cys Glu Asn Thr Pro Gly Gly His Arg Cys Ser Cys
305 310 315 320

Pro Arg Gly Tyr Arg Met Gln Gly Pro Ser Leu Pro Cys Leu Asp Val
325 330 335

Asn Glu Cys Leu Gln Leu Pro Lys Ala Cys Ala Tyr Gln Cys His Asn
340 345 350

Leu Gln Gly Ser Tyr Arg Cys Leu Cys Pro Pro Gly Gln Thr Leu Leu

172

355

360

365

Arg Asp Gly Lys Ala Cys Thr Ser Leu Glu Arg Asn Gly Gln Asn Val
 370 375 380

Thr Thr Val Ser His Arg Gly Pro Leu Leu Pro Trp Leu Arg Pro Trp
 385 390 395 400

Ala Ser Ile Pro Gly Thr Ser Tyr His Ala Trp Val Ser Leu Arg Pro
 405 410 415

Gly Pro Met Ala Leu Ser Ser Val Gly Arg Ala Trp Cys Pro Pro Gly
 420 425 430

Phe Ile Arg Gln Asn Gly Val Cys Thr Asp Leu Asp Glu Cys Arg Val
 435 440 445

Arg Asn Leu Cys Gln His Ala Cys Arg Asn Thr Glu Gly Ser Tyr Gln
 450 455 460

Cys Leu Cys Pro Ala Gly Tyr Arg Leu Leu Pro Ser Gly Lys Asn Cys
 465 470 475 480

Gln Asp Ile Asn Glu Cys Glu Glu Glu Ser Ile Glu Cys Gly Pro Gly
 485 490 495

Gln Met Cys Phe Asn Thr Arg Gly Ser Tyr Gln Cys Val Asp Thr Pro
 500 505 510

Cys Pro Ala Thr Tyr Arg Gln Gly Pro Ser Pro Gly Thr Cys Phe Arg
 515 520 525

Arg Cys Ser Gln Asp Cys Gly Thr Gly Gly Pro Ser Thr Leu Gln Tyr
 530 535 540

Arg Leu Leu Pro Leu Pro Leu Gly Val Arg Ala His His Asp Val Ala
 545 550 555 560

Arg Leu Thr Ala Phe Ser Glu Val Gly Val Pro Ala Asn Arg Thr Glu
 565 570 575

Leu Ser Met Leu Glu Pro Asp Pro Arg Ser Pro Phe Ala Leu Arg Pro
 580 585 590

Leu Arg Ala Gly Leu Gly Ala Val Tyr Thr Arg Arg Ala Leu Thr Arg
 595 600 605

Ala Gly Leu Tyr Arg Leu Thr Val Arg Ala Ala Ala Pro Arg His Gln
 610 615 620

Ser Val Phe Val Leu Leu Ile Ala Val Ser Pro Tyr Pro Tyr
 625 630 635

<210> 246

<211> 367

<212> PRT

<213> Homo sapiens

173

<400> 246

Met Gly Glu Lys Phe Leu Leu Leu Ala Met Lys Glu Asn His Pro Glu
 1 5 10 15

Cys Phe Cys Lys Ile Leu Lys Ile Leu His Cys Met Asp Pro Gly Glu
 20 25 30

Trp Leu Pro Gln Thr Glu His Cys Val His Leu Thr Pro Lys Glu Phe
 35 40 45

Leu Ile Trp Thr Met Asp Ile Ala Ser Asn Glu Arg Ser Glu Ile Gln
 50 55 60

Ser Val Ala Leu Arg Leu Ala Ser Lys Val Ile Ser His His Met Gln
 65 70 75 80

Thr Cys Val Glu Asn Arg Glu Leu Ile Ala Ala Glu Leu Lys Gln Trp
 85 90 95

Val Gln Leu Val Ile Leu Ser Cys Glu Asp His Leu Pro Thr Glu Ser
 100 105 110

Arg Leu Ala Val Val Glu Val Leu Thr Ser Thr Thr Pro Leu Phe Leu
 115 120 125

Thr Asn Pro His Pro Ile Leu Glu Leu Gln Asp Thr Leu Ala Leu Trp
 130 135 140

Lys Cys Val Leu Thr Leu Leu Gln Ser Glu Glu Gln Ala Val Arg Asp
 145 150 155 160

Ala Ala Thr Glu Thr Val Thr Thr Ala Met Ser Gln Glu Asn Thr Cys
 165 170 175

Gln Ser Thr Glu Phe Ala Phe Cys Gln Val Asp Ala Ser Ile Ala Leu
 180 185 190

Ala Leu Ala Leu Ala Val Leu Cys Asp Leu Leu Gln Gln Trp Asp Gln
 195 200 205

Leu Ala Pro Gly Leu Pro Ile Leu Leu Gly Trp Leu Leu Gly Glu Ser
 210 215 220

Asp Asp Leu Val Ala Cys Val Glu Ser Met His Gln Val Glu Glu Asp
 225 230 235 240

Tyr Leu Phe Glu Lys Ala Glu Val Asn Phe Trp Ala Glu Thr Leu Ile
 245 250 255

Phe Val Lys Tyr Leu Cys Lys His Leu Phe Cys Leu Leu Ser Lys Ser
 260 265 270

Gly Trp Arg Pro Pro Ser Pro Glu Met Leu Cys His Leu Gln Arg Met
 275 280 285

Val Ser Glu Gln Cys His Leu Leu Ser Gln Phe Phe Arg Glu Leu Pro
 290 295 300

174

Pro Ala Ala Glu Phe Val Lys Thr Val Glu Phe Thr Arg Leu Arg Ile
 305 310 315 320

Gln Glu Glu Arg Thr Leu Ala Cys Leu Arg Leu Leu Ala Phe Leu Glu
 325 330 335

Gly Lys Glu Gly Glu Asp Thr Leu Val Leu Ser Val Trp Asp Ser Tyr
 340 345 350

Ala Glu Ser Arg Gln Leu Thr Leu Pro Arg Thr Glu Ala Ala Cys
 355 360 365

<210> 247

<211> 124

<212> PRT

<213> Homo sapiens

<400> 247

Met Gly Glu Pro Asn Arg His Pro Ser Met Phe Leu Leu Leu Val
 1 5 10 15

Leu Glu Arg Leu Tyr Ala Ser Pro Met Asp Gly Thr Ser Ser Ala Leu
 20 25 30

Ser Met Gly Pro Phe Val Pro Phe Ile Met Arg Cys Gly His Ser Pro
 35 40 45

Val Tyr His Ser Arg Glu Met Ala Ala Arg Ala Leu Val Pro Phe Val
 50 55 60

Met Ile Asp His Ile Pro Asn Thr Ile Arg Thr Leu Leu Ser Thr Leu
 65 70 75 80

Pro Ser Cys Thr Asp Gln Cys Phe Arg Ala Lys Pro His Ser Trp Gly
 85 90 95

His Phe Ser Arg Phe Phe His Leu Leu Gln Ala Tyr Ser Asp Ser Lys
 100 105 110

Thr Arg Asn Glu Phe Arg Leu Pro Ala Arg Ala Asp
 115 120

<210> 248

<211> 674

<212> PRT

<213> Homo sapiens

<400> 248

Met Thr Gly Arg Glu Phe Phe Ser Arg Phe Pro Glu Leu Tyr Pro Phe
 1 5 10 15

Leu Leu Lys Gln Leu Glu Thr Val Ala Asn Thr Val Asp Ser Asp Met
 20 25 30

Gly Glu Pro Asn Arg His Pro Ser Met Phe Leu Leu Leu Val Leu

175

35

40

45

Glu Arg Leu Tyr Ala Ser Pro Met Asp Gly Thr Ser Ser Ala Leu Ser
50 55 60

Met Gly Pro Phe Val Pro Phe Ile Met Arg Cys Gly His Ser Pro Val
65 70 75 80

Tyr His Ser Arg Glu Met Ala Ala Arg Ala Leu Val Pro Phe Val Met
85 90 95

Ile Asp His Ile Pro Asn Thr Ile Arg Thr Leu Leu Ser Thr Leu Pro
100 105 110

Ser Cys Thr Asp Gln Cys Phe Arg Gln Asn His Ile His Gly Thr Leu
115 120 125

Leu Gln Val Phe His Leu Leu Gln Ala Tyr Ser Asp Ser Lys His Gly
130 135 140

Thr Asn Ser Asp Phe Gln His Glu Leu Thr Asp Ile Thr Val Cys Thr
145 150 155 160

Lys Ala Lys Leu Trp Leu Ala Lys Arg Gln Asn Pro Cys Leu Val Thr
165 170 175

Arg Ala Val Tyr Ile Asp Ile Leu Phe Leu Leu Thr Cys Cys Leu Asn
180 185 190

Arg Ser Ala Lys Asp Asn Gln Pro Val Leu Glu Ser Leu Gly Phe Trp
195 200 205

Glu Glu Val Arg Gly Ile Ile Ser Gly Ser Glu Leu Ile Thr Gly Phe
210 215 220

Pro Trp Ala Phe Lys Val Pro Gly Leu Pro Gln Tyr Leu Gln Ser Leu
225 230 235 240

Thr Arg Leu Ala Ile Ala Ala Val Trp Ala Ala Ala Ala Lys Ser Gly
245 250 255

Glu Arg Glu Thr Asn Val Pro Ile Ser Phe Ser Gln Leu Leu Glu Ser
260 265 270

Ala Phe Pro Glu Val Arg Ser Leu Thr Leu Glu Ala Leu Leu Glu Lys
275 280 285

Phe Leu Ala Ala Ala Ser Gly Leu Gly Glu Lys Gly Val Pro Pro Leu
290 295 300

Leu Cys Asn Met Gly Glu Lys Phe Leu Leu Leu Ala Met Lys Glu Asn
305 310 315 320

His Pro Glu Cys Phe Cys Lys Ile Leu Lys Ile Leu His Cys Met Asp
325 330 335

Pro Gly Glu Trp Leu Pro Gln Thr Glu His Cys Val His Leu Thr Pro
340 345 350

176

Lys	Glu	Phe	Leu	Ile	Trp	Thr	Met	Asp	Ile	Ala	Ser	Asn	Glu	Arg	Ser	355	360	365	
<hr/>																			
Glu	Ile	Gln	Ser	Val	Ala	Leu	Arg	Leu	Ala	Ser	Lys	Val	Ile	Ser	His	370	375	380	
His	Met	Gln	Thr	Cys	Val	Glu	Asn	Arg	Glu	Leu	Ile	Ala	Ala	Glu	Leu	385	390	395	400
Lys	Gln	Trp	Val	Gln	Leu	Val	Ile	Leu	Ser	Cys	Glu	Asp	His	Leu	Pro	405	410	415	
Thr	Glu	Ser	Arg	Leu	Ala	Val	Val	Glu	Val	Leu	Thr	Ser	Thr	Thr	Pro	420	425	430	
<hr/>																			
Leu	Phe	Leu	Thr	Asn	Pro	His	Pro	Ile	Leu	Glu	Leu	Gln	Asp	Thr	Leu	435	440	445	
Ala	Leu	Trp	Lys	Cys	Val	Leu	Thr	Leu	Leu	Gln	Ser	Glu	Glu	Gln	Ala	450	455	460	
Val	Arg	Asp	Ala	Ala	Thr	Glu	Thr	Val	Thr	Thr	Ala	Met	Ser	Gln	Glu	465	470	475	480
Asn	Thr	Cys	Gln	Ser	Thr	Glu	Phe	Ala	Phe	Cys	Gln	Val	Asp	Ala	Ser	485	490	495	
Ile	Ala	Leu	Ala	Leu	Ala	Leu	Ala	Val	Leu	Cys	Asp	Leu	Leu	Gln	Gln	500	505	510	
Trp	Asp	Gln	Leu	Ala	Pro	Gly	Leu	Pro	Ile	Leu	Leu	Gly	Trp	Leu	Leu	515	520	525	
Gly	Glu	Ser	Asp	Asp	Leu	Val	Ala	Cys	Val	Glu	Ser	Met	His	Gln	Val	530	535	540	
Glu	Glu	Asp	Tyr	Leu	Phe	Glu	Lys	Ala	Glu	Val	Asn	Phe	Trp	Ala	Glu	545	550	555	560
Thr	Leu	Ile	Phe	Val	Lys	Tyr	Leu	Cys	Lys	His	Leu	Phe	Cys	Leu	Leu	565	570	575	
Ser	Lys	Ser	Gly	Trp	Arg	Pro	Pro	Ser	Pro	Glu	Met	Leu	Cys	His	Leu	580	585	590	
Gln	Arg	Met	Val	Ser	Glu	Gln	Cys	His	Leu	Leu	Ser	Gln	Phe	Phe	Arg	595	600	605	
Glu	Leu	Pro	Pro	Ala	Ala	Glu	Phe	Val	Lys	Thr	Val	Glu	Phe	Thr	Arg	610	615	620	
Leu	Arg	Ile	Gln	Glu	Glu	Arg	Thr	Leu	Ala	Cys	Leu	Arg	Leu	Leu	Ala	625	630	635	640
Phe	Leu	Glu	Gly	Lys	Glu	Gly	Glu	Asp	Thr	Leu	Val	Leu	Ser	Val	Trp	645	650	655	

177

Asp Ser Tyr Ala Glu Ser Arg Gln Leu Thr Leu Pro Arg Thr Glu Ala
 660 665 670

Ala Cys

<210> 249
 <211> 10
 <212> PRT
 <213> Homo sapiens

<400> 249
 Ile Ile Ser Gly Ser Glu Leu Ile Thr Gly
 1 5 10

<210> 250
 <211> 230
 <212> PRT
 <213> Homo sapiens

<400> 250
 Val Asp Gly Ile Asp Lys Leu Asp Ile Glu Phe Leu Gln Gln Phe Leu
 1 5 10 15

Glu Thr His Ser Arg Gly Pro Arg Leu His Ser Pro Gly His Ala Ser
 20 25 30

Gln Glu Ala Thr Pro Gly Ala Asn Met Ser Ser Gly Thr Glu Leu Leu
 35 40 45

Trp Pro Gly Ala Ala Leu Leu Val Leu Leu Gly Val Ala Ala Ser Leu
 50 55 60

Cys Val Arg Cys Ser Arg Pro Gly Ala Lys Arg Ser Glu Lys Ile Tyr
 65 70 75 80

Gln Gln Arg Ser Leu Arg Glu Asp Gln Gln Ser Phe Thr Gly Ser Arg
 85 90 95

Thr Tyr Ser Leu Val Gly Gln Ala Trp Pro Gly Pro Leu Ala Asp Met
 100 105 110

Ala Pro Thr Arg Lys Asp Lys Leu Leu Gln Phe Tyr Pro Ser Leu Glu
 115 120 125

Asp Pro Ala Ser Ser Arg Tyr Gln Asn Phe Ser Lys Gly Ser Arg His
 130 135 140

Gly Ser Glu Glu Ala Tyr Ile Asp Pro Ile Ala Met Glu Tyr Tyr Asn
 145 150 155 160

Trp Gly Arg Phe Ser Lys Pro Pro Glu Asp Asp Ala Asn Ser Tyr
 165 170 175

Glu Asn Val Leu Ile Cys Lys Gln Lys Thr Thr Glu Thr Gly Ala Gln
 180 185 190

178

Gln Glu Gly Ile Gly Gly Leu Cys Arg Gly Asp Leu Ser Leu Ser Leu
 195 200 205

Ala Leu Lys Thr Gly Pro Thr Ser Gly Leu Cys Pro Ser Ala Ser Pro
 210 215 220

Glu Glu Asp Glu Gly Ile
 225 230

<210> 251

<211> 122

<212> PRT

<213> Homo sapiens

<400> 251

Val Leu Trp Arg Glu Ala Ser Ala Leu Val Leu Ser Asn Arg Leu Ser
 1 5 10 15

Ser Gly Leu Leu His Asp Leu Leu Leu Gln Pro Ala Ile His Ser Arg
 20 25 30

Leu Phe Pro Arg Arg Ser Arg Gly Leu Ser Glu Gly Glu Gly Ser Ser
 35 40 45

Val Ser Leu Gln Arg Ser Arg Val Leu Ser Ala Met Lys His Val Leu
 50 55 60

Asn Leu Tyr Leu Leu Gly Val Val Leu Thr Leu Leu Ser Ile Phe Val
 65 70 75 80

Arg Val Met Glu Ser Leu Glu Gly Leu Leu Glu Ser Pro Ser Pro Gly
 85 90 95

Thr Ser Trp Thr Thr Arg Ser Gln Leu Ala Asn Thr Glu Pro Thr Lys
 100 105 110

Gly Leu Pro Asp His Pro Ser Arg Ser Met
 115 120

<210> 252

<211> 129

<212> PRT

<213> Homo sapiens

<400> 252

Tyr Thr Phe His Thr Gln Ile Phe Leu Asp Phe Pro Met Ile Phe Leu
 1 5 10 15

Thr Val Leu Pro Leu Ala Phe Leu Phe Leu His Ser Gly Phe Tyr His
 20 25 30

Tyr Ile Ser Phe Ser Cys Leu Phe Ser Leu Ser Leu Ala Leu Phe Phe
 35 40 45

Phe Leu Asp Val Ala Thr Phe Arg Arg Pro Gly Gln Leu Phe Cys Glu

179

50

55

60

Arg Ser Val Leu Phe Asp Met Phe His Phe Gly Phe Val Ser Leu Phe
 65 70 75 80

Leu His Glu Trp Ile Gln Ala Lys His Phe Trp Ala Gly Leu Phe Ile
 85 90 95

Val Leu Pro Ser Asp Val Phe Phe Ser Val His His Leu Glu Ala Pro
 100 105 110

Asp Gly Ser Phe Pro Asn Ile Ala Lys Leu Ser Leu Ile Ile Leu Leu
 115 120 125

Arg

<210> 253

<211> 99

<212> PRT

<213> Homo sapiens

<400> 253

Gly Thr Arg Phe Pro Thr Gly Glu Thr Pro Ser Leu Gly Phe Thr Val
 1 5 10 15

Thr Leu Val Leu Leu Asn Ser Leu Ala Phe Leu Leu Met Ala Val Ile
 20 25 30

Tyr Thr Lys Leu Tyr Cys Asn Leu Glu Lys Glu Asp Leu Ser Glu Asn
 35 40 45

Ser Gln Ser Ser Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn
 50 55 60

Cys Ile Phe Phe Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile
 65 70 75 80

Thr Ala Ile Ser Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile
 85 90 95

Phe Phe Pro

<210> 254

<211> 51

<212> PRT

<213> Homo sapiens

<400> 254

Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn Cys Ile Phe Phe
 1 5 10 15

Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile Thr Ala Ile Ser
 20 25 30

WO 00/04140

180

Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile Phe Phe Pro Cys
 35 40 45

Leu Leu Ala
 50

<210> 255
 <211> 259
 <212> PRT
 <213> Homo sapiens

<400> 255
 Gly Thr Arg Phe Pro Thr Gly Glu Thr Pro Ser Leu Gly Phe Thr Val
 1 5 10 15

Thr Leu Val Leu Leu Asn Ser Leu Ala Phe Leu Leu Met Ala Val Ile
 20 25 30

Tyr Thr Lys Leu Tyr Cys Asn Leu Glu Lys Glu Asp Leu Ser Glu Asn
 35 40 45

Ser Gln Ser Ser Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn
 50 55 60

Cys Ile Phe Phe Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile
 65 70 75 80

Thr Ala Ile Ser Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile
 85 90 95

Phe Phe Pro Leu Pro Ala Cys Leu Asn Pro Val Leu Tyr Val Phe Phe
 100 105 110

Asn Pro Lys Phe Lys Glu Asp Trp Lys Leu Leu Lys Arg Arg Val Thr
 115 120 125

Lys Lys Ser Gly Ser Val Ser Val Ser Ile Ser Ser Gln Gly Gly Cys
 130 135 140

Leu Glu Gln Asp Phe Tyr Tyr Asp Cys Gly Met Tyr Ser His Leu Gln
 145 150 155 160

Gly Asn Leu Thr Val Cys Asp Cys Cys Glu Ser Phe Leu Leu Thr Lys
 165 170 175

Pro Val Ser Cys Lys His Leu Ile Lys Ser His Ser Cys Pro Ala Leu
 180 185 190

Ala Val Ala Ser Cys Gln Arg Pro Glu Gly Tyr Trp Ser Asp Cys Gly
 195 200 205

Thr Gln Ser Ala His Ser Asp Tyr Ala Asp Glu Glu Asp Ser Phe Val
 210 215 220

Ser Asp Ser Ser Asp Gln Val Gln Ala Cys Gly Arg Ala Cys Phe Tyr
 225 230 235 240

WO 00/04140

181

Gln Ser Arg Gly Phe Pro Leu Val Arg Tyr Ala Tyr Asn Leu Pro Arg
 245 250 255

Val Lys Asp

<210> 256
 <211> 22
 <212> PRT
 <213> Homo sapiens

<400> 256
 Cys Asp Cys Cys Glu Ser Phe Leu Leu Thr Lys Pro Val Ser Cys Lys
 1 5 10 15

His Leu Ile Lys Ser His
 20

<210> 257
 <211> 81
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (20)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 257
 Ala Leu Glu Asn Ser Gly Ser Pro Gly Leu Gln Asp Ser Ala Arg Ala
 1 5 10 15

His Phe Asn Xaa Ser Leu Arg Ser Phe Ser Phe Leu Arg Asn Gln Met
 20 25 30

Tyr Ile Phe Glu Leu Ser Leu Tyr Leu Glu Gly Thr Ser Phe Val Val
 35 40 45

Val Leu Leu Phe Leu Leu Ile Ser Val Ser Leu Asp Ser Pro Pro Thr
 50 55 60

Thr Lys Gly Trp Asp Ser Val Leu His Ile Trp Val Pro Leu Ile Val
 65 70 75 80

Gln

<210> 258
 <211> 77
 <212> PRT
 <213> Homo sapiens

<400> 258
 Gly His Glu Ser Ile Cys Gly Ser Cys Arg Ser Trp Ile Tyr Phe Ser
 1 5 10 15

WO 00/04140

182

Ile Arg Cys Arg Arg Arg Met Arg Pro Trp Trp Ser Leu Leu Leu Glu
 20 25 30

Ala Cys Ala Thr Cys Ala Gln Thr Gly Pro Thr Arg Ser Thr Ser Cys
 35 40 45

Thr Gln Glu Val Ser His Ser Ser Ser Thr Ala Tyr Pro Ala Pro Met
 50 55 60

Arg Arg Arg Cys Cys Leu Pro Ser Pro Arg Ser Cys Thr
 65 70 75

<210> 259

<211> 119

<212> PRT

<213> Homo sapiens

<400> 259

Lys Arg Ala Gly Val Glu Val Gly Gly Leu Val Met Ala Leu Ala Gly
 1 5 10 15

Ser Val Phe Val Leu Gly Gly Val Leu Val Leu Cys Val Glu Arg Asn
 20 25 30

Gly Glu Gly Glu Met Gly Trp Pro Gln His Leu Pro Lys Ser Gln Pro
 35 40 45

Leu Ser Pro Pro Val Ala Val Arg Arg Cys Ser Phe Glu Arg Ser Trp
 50 55 60

Ile Asp Leu Leu Val Glu Thr Ser Ser Ser Met Val Thr Cys Arg Gln
 65 70 75 80

Gln Val Gly Thr Pro Asn Gly Met Glu Gly Arg Gly Gly Gly Pro Lys
 85 90 95

Thr Thr Phe Pro Ile Arg Leu Gln Leu Ser Gly Ala Cys Ala Val Arg
 100 105 110

Pro Glu Ile Gln Trp Glu Val
 115

<210> 260

<211> 275

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (47)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (94)

WO 00/04140

183

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (192)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 260

Gln Asp Trp Lys Ala Glu Arg Ser Gln Asp Pro Phe Glu Lys Cys Met
1 5 10 15

Gln Asp Pro Asp Tyr Glu Gln Leu Leu Lys Val Thr Ile Leu Glu Ala
20 25 30

Asp Asn Arg Ile Gly Gly Arg Ile Phe Thr Tyr Arg Asp Gln Xaa Thr
35 40 45

Gly Trp Ile Gly Glu Leu Gly Ala Met Arg Met Pro Ser Ser His Arg
50 55 60

Ile Leu His Lys Leu Cys Gln Gly Leu Gly Leu Asn Leu Thr Lys Phe
65 70 75 80

Thr Gln Tyr Asp Lys Asn Thr Trp Thr Glu Val His Glu Xaa Lys Leu
85 90 95

Arg Asn Tyr Val Val Glu Lys Val Pro Glu Lys Leu Gly Tyr Ala Leu
100 105 110

Arg Pro Gln Glu Lys Gly His Ser Pro Glu Asp Ile Tyr Gln Met Ala
115 120 125

Leu Asn Gln Ala Leu Lys Asp Leu Lys Ala Leu Gly Cys Arg Lys Ala
130 135 140

Met Lys Lys Phe Glu Arg His Thr Leu Leu Glu Tyr Leu Leu Gly Glu
145 150 155 160

Gly Asn Leu Ser Arg Pro Ala Val Gln Leu Leu Gly Asp Val Met Ser
165 170 175

Glu Asp Gly Phe Phe Tyr Leu Ser Phe Ala Glu Ala Leu Arg Ala Xaa
180 185 190

Ser Cys Leu Ser Asp Arg Leu Gln Tyr Ser Arg Ile Val Gly Gly Trp
195 200 205

Asp Leu Leu Pro Arg Ala Leu Leu Ser Ser Leu Ser Gly Leu Val Leu
210 215 220

Leu Asn Ala Pro Val Val Ala Met Thr Gln Gly Pro His Asp Val His
225 230 235 240

Val Gln Ile Glu Thr Ser Pro Pro Ala Arg Asn Leu Lys Val Leu Lys
245 250 255

Ala Asp Val Val Leu Leu Thr Ala Ser Gly Pro Ala Val Lys Arg Ile
260 265 270

Thr Phe Ser
275

<210> 261
<211> 212
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (123)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 261
Leu Pro Arg His Met Gln Glu Ala Leu Arg Arg Leu His Tyr Val Pro
1 5 10 15
Ala Thr Lys Val Phe Leu Ser Phe Arg Arg Pro Phe Trp Arg Glu Glu
20 25 30
His Ile Glu Gly Gly His Ser Asn Thr Asp Arg Pro Ser Arg Met Ile
35 40 45
Phe Tyr Pro Pro Pro Arg Glu Gly Ala Leu Leu Leu Ala Ser Tyr Thr
50 55 60
Trp Ser Asp Ala Ala Ala Ala Phe Ala Gly Leu Ser Arg Glu Glu Ala
65 70 75 80
Leu Arg Leu Ala Leu Asp Asp Val Ala Ala Leu His Gly Pro Val Val
85 90 95
Arg Gln Leu Trp Asp Gly Thr Gly Val Val Lys Arg Trp Ala Glu Asp
100 105 110
Gln His Ser Gln Gly Gly Phe Val Val Gln Xaa Pro Ala Leu Trp Gln
115 120 125
Thr Glu Lys Asp Asp Trp Thr Val Pro Tyr Gly Arg Ile Tyr Phe Ala
130 135 140
Gly Glu His Thr Ala Tyr Pro His Gly Trp Val Glu Thr Ala Val Lys
145 150 155 160
Ser Ala Leu Arg Ala Ala Ile Lys Ile Asn Ser Arg Lys Gly Pro Ala
165 170 175
Ser Asp Thr Ala Ser Pro Glu Gly His Ala Ser Asp Met Glu Gly Gln
180 185 190
Gly His Val His Gly Val Ala Ser Ser Pro Ser His Asp Leu Ala Lys
195 200 205
Glu Glu Gly Ser
210

<210> 262

<211> 319

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (68)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (115)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (213)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 262

Met Ala Pro Leu Ala Leu His Leu Leu Val Leu Val Pro Ile Leu Leu
 1 5 10 15

Ser Leu Val Ala Ser Gln Asp Trp Lys Ala Glu Arg Ser Gln Asp Pro
 20 25 30

Phe Glu Lys Cys Met Gln Asp Pro Asp Tyr Glu Gln Leu Lys Val
 35 40 45

Thr Ile Leu Glu Ala Asp Asn Arg Ile Gly Gly Arg Ile Phe Thr Tyr
 50 55 60

Arg Asp Gln Xaa Thr Gly Trp Ile Gly Glu Leu Gly Ala Met Arg Met
 65 70 75 80

Pro Ser Ser His Arg Ile Leu His Lys Leu Cys Gln Gly Leu Gly Leu
 85 90 95

Asn Leu Thr Lys Phe Thr Gln Tyr Asp Lys Asn Thr Trp Thr Glu Val
 100 105 110

His Glu Xaa Lys Leu Arg Asn Tyr Val Val Glu Lys Val Pro Glu Lys
 115 120 125

Leu Gly Tyr Ala Leu Arg Pro Gln Glu Lys Gly His Ser Pro Glu Asp
 130 135 140

Ile Tyr Gln Met Ala Leu Asn Gln Ala Leu Lys Asp Leu Lys Ala Leu
 145 150 155 160

Gly Cys Arg Lys Ala Met Lys Lys Phe Glu Arg His Thr Leu Leu Glu
 165 170 175

Tyr Leu Leu Gly Glu Gly Asn Leu Ser Arg Pro Ala Val Gln Leu Leu
 180 185 190

186

Gly Asp Val Met Ser Glu Asp Gly Phe Phe Tyr Leu Ser Phe Ala Glu
 195 200 205

Ala Leu Arg Ala Xaa Ser Cys Leu Ser Asp Arg Leu Gln Tyr Ser Arg
 210 215 220

Ile Val Gly Gly Trp Asp Leu Leu Pro Arg Ala Leu Leu Ser Ser Leu
 225 230 235 240

Ser Gly Leu Val Leu Leu Asn Ala Pro Val Val Ala Met Thr Gln Gly
 245 250 255

Pro His Asp Val His Val Gln Ile Glu Thr Ser Pro Pro Ala Arg Asn
 260 265 270

Leu Lys Val Leu Lys Ala Asp Val Val Leu Leu Thr Ala Ser Gly Pro
 275 280 285

Ala Val Lys Arg Ile Thr Phe Ser Pro Arg Cys Pro Ala Thr Cys Arg
 290 295 300

Arg Arg Cys Gly Gly Cys Thr Thr Cys Arg Pro Pro Arg Cys Ser
 305 310 315

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/15849

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C12N 15/11, 15/00, 15/63; C07H 21/02, 21/04
US-CL : 536/23.1, 23.4; 435/320.1, 69.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 23.4; 435/320.1, 69.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Sequence searched SEQ ID NO:11, SEQ ID NO: 103, APS, STN, CAPLUS, terms nucleic acid, express, vector, pancreas islet cell tumors.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	US 5,849,498 A (BANDMAN et al) 15 December 1998, sequence listing.	1-10, 14-15, and 21
A	US 5,670,367 A (DORNER et al) 23 September 1997, especially sequence listing.	1-10, 14-15, and 21

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

B earlier document published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z

document member of the same patent family

Date of the actual completion of the international search

30 SEPTEMBER 1999

Date of mailing of the international search report

21 OCT 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

LI LEE

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/15849**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-10, 14-15, and 21

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

~~This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.~~

Group I, claim(s) 1-10, 14-15, and 21, drawn to isolated nucleic acid and expression system.

Group II, claim(s) 11-12 and 16, drawn to isolated polypeptide.

Group III, claim(s) 13, drawn to antibody.

Group IV, claim(s) 17, drawn to method for preventing a medical condition.

Group V, claim(s) 18-19, drawn to method of diagnosing a disease.

Group VI, claim(s) 20, 22, drawn to method for identifying a binding partner.

Group VII, claim 23, drawn to product produced by method of claim 20.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

The inventions listed as Groups I-VII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of Group I is considered to be isolated nucleic acid and expression system.

The special technical feature of Group II is considered to be isolated polypeptide.

The special technical feature of Group III is considered to be antibody.

The special technical feature of Group IV is considered to be a method for preventing a medical condition..

The special technical feature of Group V is considered to be method of diagnosing a disease.

The special technical feature of Group VI is considered to be a method for identifying a binding partner..

The special technical feature of Group VII is considered to be product produced by method of claim 20.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

There are 71 genes, from gene Nos 1-71.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The 71 genes have different nucleic acid sequences and they are from different cell. Therefore they lack same special technical features.